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THE CYSTOSCOPIC STUDY OF UROLOGIC CONDITIONS IN CHILDREN

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Abnormalities of the urinary tract of children, apparently, are not prevalent.[1] But accurate methods of diagnosis are almost universally neglected. The majority of these little patients are unable to describe their symptoms or to indicate the type and degree of their suffering. When indications for accurate investigation do arise, one hesitates to subject a helpless baby to painful methods of study. The real anxiety should lie in regard to the wisdom of our clinical interpretation. It is probably a greater error to miss making an early diagnosis through neglect of proper examination than to mistake the indication and unnecessarily subject the child to the examination. These considerations are particularly prominent in urologic diagnosis, which so frequently requires an anesthetic and cystoscopy. Nevertheless, if technically possible and perfectly safe, is it logical to neglect in children those methods unhesitatingly used for the diagnosis of similar conditions in adults?[2]

In recent years the perfection of small caliber instruments has been such as to open for the direct application to the field of urology in children all of the knowledge and experience gained in the development of general urology during the past twenty or twenty-five years. Personal experience teaches me that it is a simple procedure to cystoscope the bladder and catheterize the ureters of girls of whatever age, and of boys over 4 or 5 years. For little fellows under 4 an external urethrotomy, which in itself is not mutilating or dangerous, permits of the examination.

Such an examination, which of necessity assumes the nature of a minor operation, must not be undertaken prematurely. The indications should be definite and most carefully considered. Pyuria and hematuria are signs readily recognized. Careful microscopic and bacteriologic urinary studies need no emphasis. But the value of urethral catheterization is too often overlooked. It will inform one of the condition of uncontaminated bladder urine, of the bladder capacity

and of the existence of urinary residual. This latter has a certain pathognomonic significance in boys. In the absence of congenital or traumatic stricture, or of urethral stone, the finding of a residual will be strongly indicative of posterior urethral valve formation, an early diagnosis of which must often mean the preservation of the child's life. Furthermore, the insertion of an urethral catheter permits of cystography which will demonstrate the bladder outline and position, and occasionally, insufficient ureteral papillae with hydroureters and hydronephrosis, or rarely a diverticulum. For purposes of bladder catheterization in infants a No. 5 or 6 F. Albarran flute-end ureteral catheter is ideal, and will be found of service in older children, particularly boys, who may thus be catheterized without pain or difficulty. In this connection may be emphasized the neglect of obstetricians and pediatricians to meatotomize their patients when this is plainly indicated. The virtue of circumcision has proper recognition, but not enough attention is paid to the meatus of the male urethra. Yet congenital narrowing at this point is quite common and undoubtedly frequently leads to urinary disturbances in infancy and childhood.

In addition to urinary and urethral studies, the evidence of roentgen ray and of renal functional studies should precede the decision to submit the case to cystoscopy. The roentgen ray will demonstrate the size, shape and position of kidneys much more reliably in children than in adults.[4] In the latter it has small value for this purpose, but in children, because of the better definition and greater accuracy, it is often diagnostic, and plain pictures in suspected cases should never be neglected. Calculi occur in the kidneys, ureters, bladder and urethra in early life as well as later, and I believe it a safe rule, though expensive, to make roentgenograms of the whole urinary tract of every child with a pyuria or hematuria. This modern method of diagnosis is woefully neglected by general practitioners and others, if we may judge by the proportion of stone cases in which the patient voids pus and blood for years, being mistreated for a "cystitis" until some one finally stumbles on roentgenography.

Functional studies are as illuminating in suspected urinary disease in children as in adults. Phenolsulphonephthalein is probably the most practical test for total function, but can only supplement a careful chemical, microscopic and bacteriologic study. Repeated tests should be made because the possibilities of error are even greater than in adults. Reduction in function signifies bilateral disturbance, but a normal output has a negative value inasmuch as one kidney may be affected or even completely destroyed, or both may be slightly damaged.[5] Retention tests are rarely indicated.

When such preliminary investigation indicates a probable vesical or renal lesion, which is otherwise uncertain, cystoscopy and ureteral catheterization should be unhestiatingly advised irrespective of the patient's age. The following is a partial report of twenty-six children cystoscoped largely in conformity to this rule; the youngest boy was 3 years, the youngest girl, 11 months of age.

PYURIA IN GIRLS

In a small series of cases of pyuria in girls ureteral catheterization was not undertaken in the belief that it was absolutely required, nor solely for purposes of therapy; we were interested mainly in determining the exact location of the infection and then in applying modern methods of treatment. In view of the chaos in medical ideas regarding hematogenous, lymphogenous and ascending routes of infection in pyelocystitis, the findings have a tremendous significance. The average age was 6 years, the youngest 11 months; the oldest, 14 years. Of the twelve cases, six were acute or subacute infections and six chronic. In three of the acute and three of the chronic cases, infection was limited to the bladder; microscopic and cultural studies of the catheterized kidney urines were negative. There was cystoscopic evidence of bladder inflammation in all twelve cases. Infection was confined to the left side in two and was bilateral in four of the six pyelites. The total phenolsulphonephthalein was normal in all. In other words, of twelve cases of clinical pyelocystitis, simple cystitis was present in 50 per cent., bilateral pyelitis with cystitis in only 33 per cent., and unilateral pyelitis with cystitis in only 16 per cent. *Bacillus coli communis* was cultivated from the urine in all but one case in which a pure staphylococcus was secured. In all of the ureteral catheterizations silver nitrate in strengths of ¼ to 2 per cent. was used as pelvic lavage before the withdrawal of the catheters.

The negative findings in respect to kidney involvement in 50 per cent. of the cases should be forcefully brought to the attention of those who maintain that infection is blood-borne in practically 100 per cent. of cases of cystopyelitis of infancy.[6] The possibility is admitted that the kidneys may have been infected and have cleared themselves before the examination, but this seems very unlikely, particularly in the acute cases, three of which showed repeatedly negative urines from both kidneys. The quick and remarkable benefit following silver nitrate lavage of the kidneys, when infected, is worthy of attention. The procedure takes from five to ten minutes, and, as it was done under primary gas and oxygen anesthesia, without trauma or any bad effects whatever afterwards, no hesitancy is felt in strongly advising this logical procedure in those cases resisting the ordinary method of treatment.[7]

Careful urologic studies have permitted accurate recognition of other types of urinary disease in children. Caseocavernous renal tuberculosis (surgical) is very rare in children. Morris found none under 10 years. The youngest case in the author's experience is 13 years (ten cases under 18 have been seen, two of which are remarkable examples of autonephrectomy). Surgery for renal tuberculosis, therefore, can rarely be applied in children. The kidneys, however, are involved in 100 per cent. of miliary tuberculosis, which is twice as frequent in children as in adults. Two cases of this type with pronounced bilateral renal involvement have been diagnosed, ages of patients 3 and 5 years, respectively, both terminating fatally.

Calculus formation has been recognized four times, left nephrolithiasis in a boy of 4 years (with congenital posterior urethral valve), large urethral calculus in a boy of 5 and large bladder stones in boys of 3 and 4 years, respectively.

Acute hemorrhagic nephritis has been studied cystoscopically in two girls of 6 and 10 years.

Urologic investigation with diagnosis has been made of a large retroperitoneal sarcoma, a large hypernephroma and an insufficient horseshoe kidney, all of these patients coming to operation or necropsy.

Three small boys, aged 3, 4 and 5 years, with symptoms of prostatism and residuals of 80, 320 and 110 c.c., have been subjected to examinations (the youngest required external urethrotomy) which revealed valve-like obstructions in the posterior urethra. This interesting anomaly has been recently emphasized.[8] The writer, while resident in urology at the Johns Hopkins Hospital, had an opportunity to assist Dr. Young in the surgical treatment of two such patients and to observe the striking effects on the ureters and kidneys in a third case which came to necropsy. The occurrence of three additional cases in his own practice, in two of which the patients have been operated on, in less than four years supports the feeling that the condition is more common than is generally realized.

This brief outline of a relatively short experience will serve to support the contentions of this paper: First, a complete urologic study (cystoscopy and ureteral catheterization) is technically possible in children irrespective of sex or age; second, occasionally, clinical manifestations demand for their correct interpretation such a study, and the benefit of logical treatment, possible because of an accurate diagnosis, justifies its seemingly radical nature; third, in none of the cases to which these principles have been applied has there been any untoward consequences or disagreeable complications. The results in every instance have justified the procedure.

516 Sutter Street.

REFERENCE FOOT NOTES

1. The apparent rarity of urologic diseases other than bladder stone, colon bacillus pyuria and renal tumor, is supported by a review of the pediatric literature. Nevertheless, there are many reasons for inaccurate diagnosis of affections of the urinary tract in children, and doubtless many urologic cases are overlooked.

2. The literature contains few references to the practical use of the cystoscope in early childhood. Only ten years ago Ditze (Ditze: Lehrbuch der Kystoskopie, 1907, p. 97) was the first to call attention to it and reported successful cystoscopies in a few instances of males as young as 8 years, and advised perineal urethrotomy for its use in younger males. A year later, Portner (Portner: Deutsch med. Wchnschr. **43**: 1908) reported successful cystoscopies and ureteral catheterization in a few cases (youngest boy 8 years). Seven years ago Beer (Beer, Edwin: Cystoscopy and Ureteral Catheterization in Young Children) reported his experiences, successfully catheterizing the ureters of a girl and cystoscoping the bladder of a boy, both 5 years of age. The method, however, has not become general. Last year, Quimby (Quimby, W. C.: Pyelitis in Children, J. A. M. A. **68**:591, 1917) referred to its occasional use in treating pyelitis in infancy. In February, 1918, Hyman (Hyman, A.: Surgical Diseases of the Urinary Tract in Children, Am. J. Dis. Child. **15**:116, 1918) reviews his and Beer's experiences in thirty cases subjected to careful urologic study, and commends the method highly.

3. Brown-Buerger 21 F. double catheterizing, and 16 F. single catheterizing cystoscopes have been used. The larger size may be safely used in girls of 2 years or older, and has the advantage of shortening the period of examination, since both ureters may be quickly catheterized and the instrument withdrawn, leaving the catheters in place. With the single catheterizing instrument, only one side may be explored at a time, and the instrument must either be left in until a specimen has been collected and treatment given before the catheter can be withdrawn and another passed in the opposite side, or the instrument must be withdrawn and reinserted for the second catheterization. In case silver nitrate has been injected for purposes of pelvic lavage, the bladder contents are often so clouded as to render catheterization of the other ureter quite difficult, and this cloudiness may persist for several minutes. In order to shorten the period of anesthetization, the 16 F. cystoscope may be withdrawn after one catheter has been passed, leaving this in place and the instrument immediately reinserted alongside of this ureteral catheter in the urethra. The opposite ureter may then be catheterized and the cystoscope withdrawn, leaving both ureteral catheters in place. The anesthesia may be stopped immediately on the removal of the cystoscope, and the specimens collected and treatments given with the child awake. Nitrous oxid and oxygen anesthesia has been found most satisfactory, as it is not followed by nausea or renal inhibition.

In order to avoid bladder contamination of kidney specimens, it has been the custom to have an assistant flush each catheter with a steady stream of sterile water by means of a syringe up to the actual insertion of the catheter tip into the ureter.

4. In pediatric textbooks little if any reference is made to roentgenology of the urinary tract. Rotch's recent book, "The Roentgen Ray in Pediatrics," makes no mention of it.

5. Chromocystoscopy (with indigo carmin, recommended by Hyman, Footnote 2) would appear to be of practical value in children in determining the relative function of the two kidneys when ureteral catheterization is not done. But the normally late appearance of the dye prolongs the anesthesia beyond the period of justification for the small amount of information derived. After ureteral catheterization intravenous phenolsulphonephthalein is undoubtedly preferable, and for the same reasons as apply in the adult. Much more reliable

information is given by a careful study of the separate urines, and occasionally by pyelography. The indications for the use of chromocystoscopy is the same for children as for adults, namely, where ureteral catheterization is impossible.

6. In spite of the overwhelming opposition of clinical facts, many writers still favor the hematogenous, or descending, theory of kidney infection in children. This is thought to occur first as a bacterial invasion of the lymphatics from the intestinal tract or other focus. The organisms then pass into the blood and are carried to the kidneys. They may be excreted without damaging the kidney, or may cause pyelitis. The preponderance of cases in girls is explained (Smith, R. M.: Pyelitis of Infancy, Am. J. Dis. Child. **12**:235, 1916) by the fact that the vulva, urethra and vagina are the breeding places for bacteria, which enter the lymphatics, blood and finally the kidneys, but do not ascend through the urethra. The argument against ascending infection, that colon bacilli have never been shown to pass up a normal unobstructed ureter, meets opposition in some recent experimental work. By cystography in perfectly healthy small boys it has been shown that the bladder fluid could regurgitate to the kidney, beautiful ureteropyelograms being frequently obtained after simple collargol distention of the bladder. The simple intracystic injection by Helmholz (Helmholz, H. F.: Ascending Infection of the Urinary Tract, Arch. Pediat. **35**:375, 1918) of a colon bacillus isolated from spontaneous infection in a rabbit, produced pyelitis in ten of fifteen rabbits. Facts like these two, the overwhelming clinical evidence and the absence of kidney infection on ureteral catheterization in 50 per cent. of the author's cases, lead one to believe that the ascending route is by far the more frequent in female children.

7. It is not the purpose of this paper to give in detail the histories and findings so strongly favoring the idea of the frequent occurrence of an ascending route of infection; nor the very favorable results so highly commending the logical method of treatment by pelvic lavage.

8. This anomalous condition has been more recently described and emphasized by Lowsley (Lowsley, O. S.: Congenital Malformation of the Posterior Urethra, Ann. Surg. **60**:733, 1914) who gives complete bibliography.

STUDIES ON THE MAMMARY GLAND

V. THE EFFECTS OF INANITION ON THE DEVELOPING MAMMARY GLANDS IN MALE AND FEMALE ALBINO RATS FROM BIRTH TO TEN WEEKS OF AGE *

J. A. MYERS, M.S., PH.D.
MINNEAPOLIS

In a previous work[1] attention was called to the fact that the postnatal development of the milk ducts probably depends to some extent on the body weight of the animal. The present work is an attempt to show: (1) to what extent the postnatal development of the milk ducts may be altered by changes from the normal body weight of the animal; (2) the effect of severe inanition on the development of all parts of the mammary gland; (3) the recovery of the mammary gland in animals on refeeding after inanition.

MATERIAL AND TECHNIC

The material used in this study was kindly presented to me by Dr. C. A. Stewart,[2] who made a study on the central nervous system of the same animals. The series of rats used included more than twenty males and females ranging in age from birth to 10 weeks (one or two individuals being somewhat older). The control rats were allowed to grow normally while the test animals were held at or near birth weight for various periods of time. This was done by removing the test rats from the mother at successive periods. To restrict the weight after weaning the rats were fed small amounts of whole wheat (Graham) bread, soaked in whole milk. After such periods of starving, a few females were refed until they reached the weight of the normal or control animal at the time of killing.

In most cases comparisons were made from test and control rats of the same litter. However, in some cases the glands in a control rat of the same litter as the test animal were not available; hence it became necessary to compare the glands of the test rats with those of apparently normal animals of other litters of the same age. In both test and control animals some of the glands were sectioned serially, the sections being 10 microns in thickness, and stained in Heidenhain's iron hematoxylin stain or Mallory's connective tissue stain.

So far as possible the glands were removed from the epidermis with the connective tissue layers of the skin and cleared according to the method used

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* From the Institute of Anatomy, University of Minnesota.

1. Myers, J. A.: Studies on the Mammary Gland. III. A Comparison of the Developing Mammary Glands in Male and Female Albino Rats from the Late Fetal Stages to Ten Weeks of Age, Anat. Rec. **13**: 1917 (Abst. in Anat. Rec. **11**: 1917).

2. Stewart, C. A.: Weights of Various Parts of the Brain in Normal and Underfed Albino Rats at Different Ages, J. Comp. Neurol. **25**:511, 1918.

by Lane-Claypon and Starling.[3] In rats held at slightly above birth weight, however, it was extremely difficult to remove the connective tissue layer of the skin without tearing it or injuring the mammary glands.

OBSERVATIONS

1. *Effects of Inanition.—Newborn.*—In a normal new-born female albino rat of about 4.5 gm., the mammary glands (Fig. 1) show a considerable branching of the milk ducts. (Only two of the six glands on each side are shown in the figure. For complete description, see Myers.[4]) Quaternary ducts are present in all of the glands examined

Fig. 1.—Drawn from a cleared preparation (internal view) of a new-born female albino rat (weight 4.5 gm.) to show distribution and relations of ducts of right abdominal gland (A), and right first inguinal gland (B) × 5. A.n., abdominal nipple; I.n.1, first inguinal nipple; p.d., primary duct; s.d., secondary duct; t.d., tertiary duct; tr.d., terminal duct; e.b., end-bud.

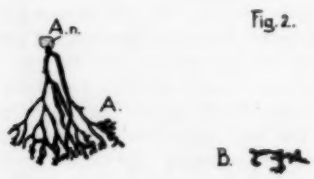

Fig. 2.—Same as Figure 1, but from animal that was starved so as to weigh only 3.6 gm. at eight days, × 5. The greater part of the first inguinal gland (B) was lost in making the cleared preparation.

and in most individuals the fifth, sixth and even the seventh divisions of the ducts have occurred. Terminal end-buds are fairly prominent. Collateral ducts (short side branches) are present in small numbers and are chiefly located near the free end of the ducts of a gland. They are very rare on any of the main ducts nearer the nipple than

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3. Lane-Claypon, Miss J. E., and Starling, E. H.: An Experimental Inquiry Into the Factors which Determine the Growth and Activity of the Mammary Glands, Proc. Roy. Soc. M. and S., Series B **77**: 1906.

4. Myers, J. A.: Studies on the Mammary Gland. I. The Growth and Distribution of the Milk Ducts and the Development of the Nipple in the Albino Rat from Birth to Ten Weeks of Age, Am. J. Anat. **19**: 1916 (Abst. in Anat. Rec. **10**:20, 1916). Myers, J. A.: Studies on the Mammary Gland. II. The Fetal Development of the Mammary Gland in the Female Albino Rat, Am. J. Anat. **22**: 1917 (Abst. in Anat. Rec. **11**:390, 1917).

the quaternary ducts. The branching of the milk ducts in the new-born male is essentially the same as in the female.

It was previously shown[5] that the nipple of the new-born female albino rat is only slightly elevated above the surface of the surrounding epidermis, and that in some cases there is around the nipple a shallow sulcus, which was regarded as a remnant of the mammary pit of the fetus. The epidermis covering the nipple is considerably thickened. Deep in the sulcus surrounding the nipple lies the projection of the "epithelial hood." Near the highest part of the nipple may be seen a slight excavation which represents the position of the future milk pore and intra-epidermal part of the primary duct. The lumina

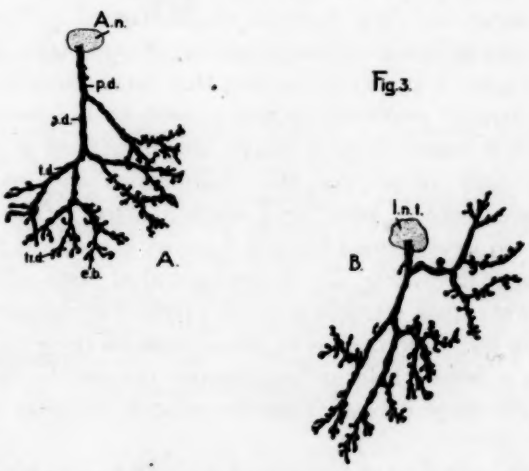

Fig. 3.—Same as Figure 1, but from a normal female of 3 weeks (weight 30 gm.), × 5.

of the milk ducts are not completely formed, being best developed from the secondary or tertiary ducts to the free ends of the terminal ducts. As the primary duct is approached the lumen presents an irregular outline, while nearer the attached end of the duct it is represented by isolated lacunae. Near the surface there appears at this stage no trace of a lumen. From the secondary ducts to the end of the terminal ducts the epithelial walls are composed of two fairly definite layers of cells. From the secondary ducts toward the surface the cells gradually show an irregular arrangement until near its attached end the primary duct is represented by a solid cord of epithelial cells.

5. Myers, J. A.: The Histology of the Mammary Gland in the Male and Female Albino Rat from Birth to Ten Weeks of Age, Am. J. Anat. To be published (Abstr. in Anat. Rec. **14**:46, 1918.

Eight Days (Held at Birth Weight).—In a female that was held at birth weight for eight days the milk ducts (Fig. 2) show considerably less branching than those in a normal rat of seven days. They show, however, a slightly greater tendency to branch than the ducts of the normal new-born rat. The new branches are confined chiefly to the free end of the gland; however, an occasional collateral duct appears on the secondary and tertiary ducts.

When examined macroscopically the nipples appear more prominent than in the new-born. The nipple has, therefore, grown somewhat in spite of the fact that the gross body weight remains the same as at birth, or has even decreased.

Eighteen, Twenty and Twenty-One Days (Held at Birth Weight).—Figure 3 shows the milk ducts of the abdominal and first inguinal glands of a normal female albino rat of twenty-one days. When compared with Figure 1 it will be noticed that from birth to twenty-one days a considerable proliferation and growth of the ducts has taken place. Figure 4, drawn from a female albino rat held at birth weight for eighteen days, shows that the proliferation and growth of the milk ducts have been retarded to a marked extent. The ducts show very little or no development beyond those of the animal held at birth weight for eight days (Fig. 2), or the normal at birth (Fig. 1). The milk ducts in the male rat held at birth weight for eighteen days show approximately the same degree of retardation as those in the female. The ducts in a female held at birth weight for twenty days (Fig. 5) show about the same extent of development as those in the eighteen day stage.

Microscopic sections through the glands of a female show that in spite of the fact that the animal was held at birth weight the nipple has developed beyond the new-born stage. Its development has been considerably retarded, however, as it is much less prominent than the nipple of normal animals of corresponding age. The stimulus that causes the rapid growth of the nipple in normal rats about the second week has apparently been affected by the inanition, as the rapid growth of the gland at this stage has been inhibited. The nipple is considerably elevated above the surface (Fig. 12) of the surrounding epidermis. Partially surrounding the basal part of the nipple is the sulcus, deep in which may be seen the projection of the epithelial hood. This projection shows very little or no further development than appears in the new-born. The processes which appear on the projection of the normal animals of eighteen to twenty-one days (similar to those shown in Fig. 14) are very small in the starved rat. The external opening or milk pore appears near the highest part of the nipple, the lumen leading from this into the intra-epidermal

part of the primary duct is quite shallow and is not continuous with the lumen of the primary duct proper. A cord of epithelial cells separates these two lumina, as is the case in normal animals until the second week of postnatal life is reached. The part of the attached end of the primary duct deep to the intra-epidermal portion is, therefore, without a lumen, but as one follows the sections toward the

Fig. 4.—Same as Figure 1, but starved so as to weigh only 5 gm. at 18 days, × 5.

free end a lumen appears which is more regular in outline than in the new-born state, but is less well developed than in normal or control animals of same age as the test rats. Traced from the primary duct toward the free end of the system of ducts, the lumen presents the same general appearance as in normal animals of the same age except that it is somewhat smaller in caliber. The walls of the milk ducts beyond the primary duct possess the two layers of epithelial cells found in normal animals. Through the free end of the primary duct the cells are more irregularly arranged.

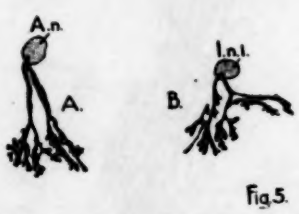

Fig. 5.—Same as Figure 1, but starved so as to weigh only 5 gm. at 20 days, × 5.

Thirty-Three Days (Weight Restricted to 9.4 Gm.).—The female control animal reached a weight of 49 gm. at the end of the thirty-third day. The milk ducts, as shown in Figure 6, have grown and proliferated very rapidly since the 21-day stage (Fig. 3). While there is no overlapping between the ducts of adjacent glands, the ducts of the second thoracic gland are very nearly in apposition with those of the first and third thoracic glands. As seen in Figure 6, the ducts of the abdominal and first inguinal glands very nearly meet. Only a small interspace exists between the ducts of the first and second

Fig. 6.—Drawn from a cleared preparation (internal view) of a normal female albino rat of 33 days (weight 49 gm.) to show distribution and relations of ducts of right abdominal gland (A), and right first inguinal gland (B), ×5 A.n., abdominal nipple; L.n.1, first inguinal nipple; p.d., primary duct; s.d., secondary duct; t.d., tertiary duct; tr.d., terminal duct; e.b., end-bud; L., lymph node.

inguinal glands. An examination of the glands of the underfed test animal, whose body weight never exceeded 9.4 gm., reveals the fact that the milk ducts are still in a very primitive state of development (Fig. 7). In spite of the fact that the body weight of this animal was allowed slightly to exceed that of a normal animal of one week, the milk ducts do not show as extensive proliferation and growth as those in a normal animal of one week. In fact some of the glands of this animal appear very slightly or no better developed than those in normal animals at birth.

Fig. 7. Same as Figure 6 but from test animal of same litter which was starved so as to weigh only 9.4 gm. at 33 days, × 5

The study of microscopic sections shows the nipple slightly more elevated above the surface of the surrounding integument than in test animals of 18 to 21 days of age. The sulcus around the nipple presents approximately the same depth as in the preceding stage. The projection of the "epithelial hood" is in a rudimentary state of development. The sections show rather numerous projections extending

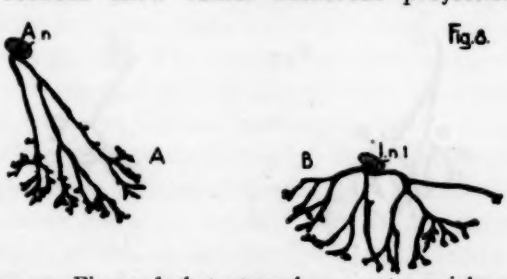

Fig. 8.—Same as Figure 1, but starved so as to weigh only 10 gm. at 38 days, × 5.

inward from the epidermis covering the nipple. The lumen of the intra-epidermal part of the primary duct has deepened somewhat, but is not quite continuous with that of the primary duct proper.

Thirty-Eight Days (Weight Restricted to 10 gm.).—In a female of 38 days, whose body weight never exceeded 10 gm., the milk ducts show a very slight increase in length over those in the normal newborn. In Figure 8 it will be observed that there is an occasional col-

lateral duct branching from the secondary and tertiary ducts. Generally, however, collateral ducts are not numerous on any part of a system of ducts. Compare this and preceding with normal at 1 week (about 10 gm.).

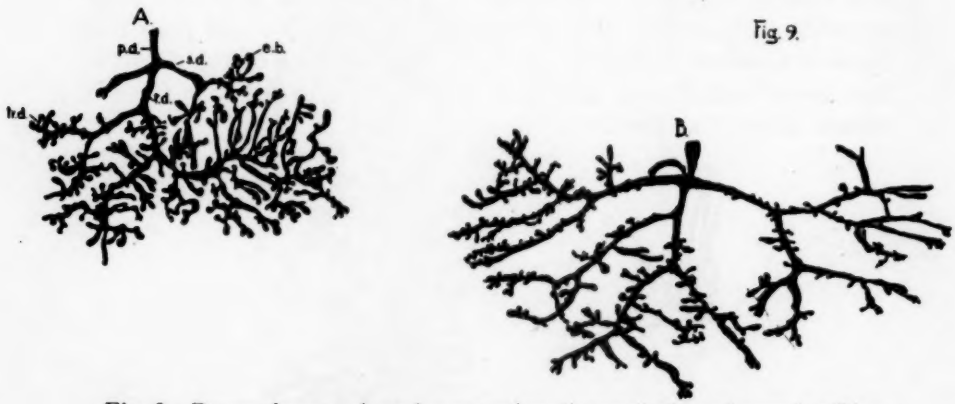

Fig. 9.—Drawn from a cleared preparation (internal view of a male albino rat of 58 days, weight 96 gm.) to show distribution and relations of ducts of right abdominal gland (A), and right first inguinal gland (B), × 5. In the illustration p.d. = primary duct; s.d., secondary duct; t.d., tertiary duct; tr.d., terminal duct; e.b., end-bud; L., lymph note.

Fifty-Eight Days (*Weight Restricted to 10.9 gm.*).— The male control animal weighed 96 gm. at the age of 58 days. The milk ducts (Fig. 9) show about the normal amount of branching for males of this age, there being a failure of the ducts to respond to the puberty

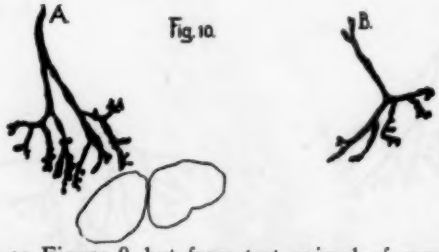

Fig. 10.—Same as Figure 9, but from test animal of same litter which was starved so as to weigh only 10.9 gm. at 58 days, × 5.

changes occurring in the female.[1] In the test animal with a body weight of 10.9 gm. the milk ducts (Fig. 10) show approximately the same degree of retardation as those of the female. In other words, the ducts show about the same number of branches, and are, in general, of the same size as at the time of birth, notwithstanding the fact that the body weight of the test animal is more than double that of the new-born.

Fifty-Eight Days (Weight Restricted to 15.5 Gm.).—This animal was allowed to reach a body weight equal to that of a normal rat of 2 weeks. The increase in weight over the last stage, however, had no apparent effect on the growth or proliferation of the milk ducts, as they do not appear noticeably different from those of an animal of the same age with a smaller body weight.

The nipples in microscopic sections show no greater elevation than in animals held at 9.4 gm. for thirty-three days. Normal rats with a body weight of 15.5 gm. possess nipples much more elevated than underfed animals of the same weight. It appears, therefore, that during underfeeding very little of the weight added to the body between the 33 and 58-day stages is accompanied by growth of the mammary glands. The systems of milk ducts in the 58-day underfed rats show the same structure as earlier described stages. The lumina do not communicate with the exterior, owing to the cord of epithelial cells persisting between the lumen of the intra-epidermal part of the primary duct and that of the primary duct proper. The lumen of the intra-epidermal part of the primary duct contains débris derived from the process of desquamation and delamination in the formation of the lumen.

Sixty-Five Days (Weight Restricted to 8.5 Gm.).—It was shown earlier[4] that the milk ducts of the normal female albino rat undergo a tremendous proliferation during the eighth or ninth week — the time when puberty usually appears. The control animal used in the present study had reached a body weight of 82.5 gm. on the sixty-fifth day, the time of killing. The ducts of the mammary glands have developed to such an extent that there is a decided overlapping of the ducts of adjacent glands. The ducts of the thoracic glands have overlapped so as to form on each side a continuous arborization of ducts which extends from the cephalic portion of the first thoracic to the caudal part of the third thoracic gland. The ducts of the abdominal and inguinal glands on each side likewise show a continuous arborization which extends from the cephalic part of the abdominal to the most caudal ducts of the second inguinal gland. In the test animal, which was held at 8.5 gm. by underfeeding, no such development has occurred. The milk ducts are somewhat longer than those in the new-born, but otherwise there is no apparent difference.

Microscopic sections through the nipples of test and control animals show a considerable contrast. The nipple of the control has reached a considerable elevation and has taken on a somewhat conical form. The projection of the "epithelial hood" presents numerous processes, while in the central part of the attached end of the projection degenerative changes are in progress. The system of milk

ducts communicates freely with the exterior through the milk pore. The nipple of the test rat, on the other hand, is only slightly elevated and does not present a conical form. The projection of the "epithelial hood" is very rudimentary. There is a very slight communication of the system of milk ducts through the milk pore, the lumen of the intra-epidermal part of the primary duct not being completely formed.

Seventy Days (Weight Restricted to 16.5 Gm.).—The milk ducts of this female rat show nothing different from that which has been described in the foregoing stages. The ducts remain in a very poorly developed state.

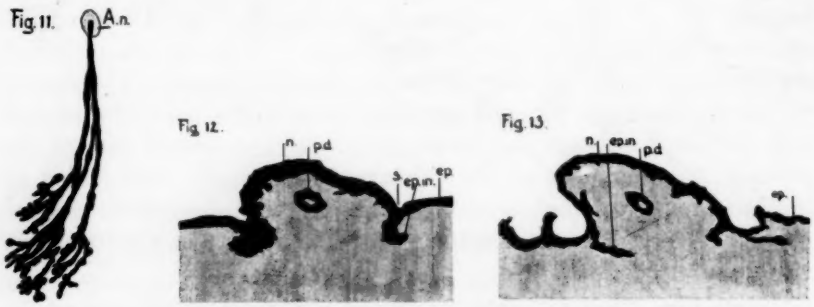

Fig. 11.—Same as Figure 1, but from a test animal which was starved so as to weigh only 8.5 gm. at 65 days, × 5.

Fig. 12.—Drawn from a section through the nipple of a female albino rat. Starved so as to weigh only 5 gm. at 18 days, × 66⅔; ep., epithelium; ep.in., epithelial ingrowth or hood; n., nipple; p.d., primary duct; s., sulcus around base of nipple.

Fig. 13.—Drawn from a section through the nipple of a female albino rat. Starved so as to weigh only 16.5 gm. at 70 days, × 66⅔. Compare with Figure 14. ep., epithelium; ep.in., epithelial ingrowth or hood; n., nipple; p.d., primary duct; s., sulcus around base of nipple.

Microscopic sections (Fig. 13) show the nipple remaining at about the same degree of elevation as in the 33-day underfed rats. The projections of the "epithelial hood" have failed to develop beyond the stages previously described. A slight communication has appeared between the lumen of the intra-epidermal part of the primary duct and that of the primary duct proper. Therefore, the lumina of the system of ducts have a common opening to the exterior through the milk pore. This condition normally is present in the rat at the end of the second week of postnatal life; however, it is usually not until the fifth or sixth week that this communication has attained its normal caliber. The two-layered arrangement of the epithelial walls of the milk ducts persists. No parts resembling developing alveoli have been observed, and there is no indication of lobulation. The mantle layer

(which immediately surrounds the milk ducts) of the stroma is thinner than in normal rats of the same age. The true stroma which normally contains such an abundance of fat is nearly or quite free from fat. The entire stroma appears much more cellular and less vascular than in normal animals of the same age.

2. *Effects of Refeeding.*—This part of the present article should be regarded only as a preliminary report, as further work now in progress will be presented at a later time.

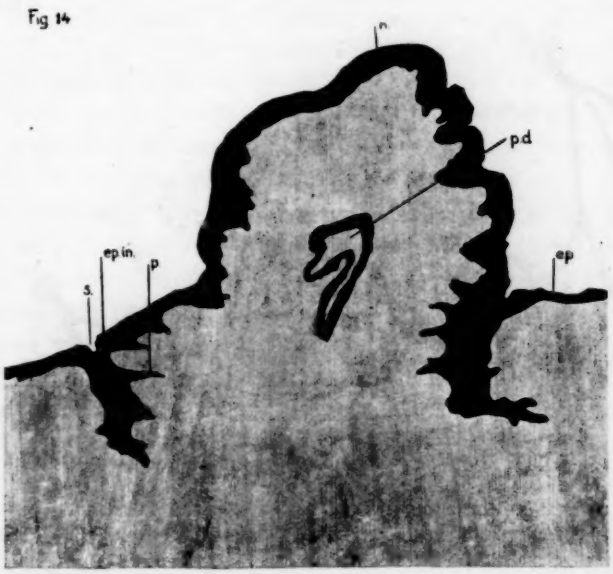

Fig. 14.—Drawn from a section through the nipple of a normal female albino rat of nine weeks, ×66⅔. Labeling same as in Figure 13. Compare with Figure 13.

Seventy days (weight restricted to 10 gm. for nineteen days, then placed on normal diet. Weight 42 gm.): The glands of the control animal show the normal extensive development which occurs about the time of puberty described in an earlier article.[4] From the gross body weight of the test rat one might expect to find the milk ducts in a stage of development nearly equal to those of a normal rat of 4 or 5 weeks. This, however, is not the case. As shown in Figure 15, the ducts have grown and proliferated considerably beyond those in animals of 18 to 21 days held at approximately birth weight (Figs. 4 and 5). The ducts of this animal are quite comparable in their extent of development with those of a normal rat of about 3 weeks (compare with Fig. 3).

Microscopic sections show that the nipple in the refed animals possesses a diameter somewhat greater than that of the underfed animal of 70 days. The elevation is approximately the same. The refeeding has apparently had an effect on the development of the projection of the "epithelial hood," as this projection now presents a somewhat greater diameter than in animals before the refeeding; besides, it possesses a number of processes, as does also the inner surface of the epidermis covering the nipple. These processes are somewhat larger than those seen in the starved rats (Figs. 12 and 13).

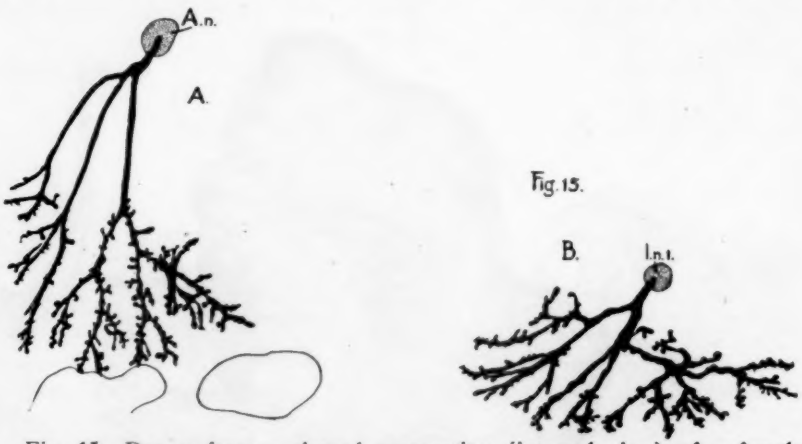

Fig. 15.—Drawn from a cleared preparation (internal view) of a female albino rat to show distribution and relations of ducts of right abdominal gland (A), and first inguinal gland (B), × 5. This animal was starved so as to weigh only 10 gm. at the nineteenth day of life, after which it was placed on normal diet until 70 days old, when it weighed 42 gm. A.n., abdominal nipple; I.n.1, first inguinal nipple; p. d., primary duct; s.d., secondary duct; t.d., tertiary duct; tr.d., terminal duct; e.b., end-bud.

The milk ducts have increased somewhat in diameter, but the epithelium of the walls is arranged in the two usual layers except the intra-epidermal part of the primary duct, which is lined with the stratified squamous type. The epithelial cells appear somewhat larger than in animals that have not been refed and mitotic figures are not uncommon. The stroma does not appear as cellular as when the animals were being starved. Moreover, a considerable amount of fat has made its appearance in the true stroma.

One hundred and twelve days (weight restricted to 10 gm. for nineteen days; then placed on normal diet until gross body weight reached 85 gm., that of control killed at 70 days): This female rat was from same litter as the preceding. Figure 16 shows that the milk ducts have undergone a considerable development beyond those of the sister killed at 70 days, with a body weight of 42 gm. They

have not, however, reached the same degree of development as those of the control killed at 70 days with a corresponding body weight. In the control animal, the ducts of the thoracic glands overlap so as to form a continuous arborization on each side. The abdominal and inguinal glands also form on each side a continuous mass of gland tissue. In the test rat, the ducts of the abdominal and inguinal glands are nearly in apposition and only rarely is there an overlapping. Collateral ducts are much more numerous on the secondary, tertiary and quaternary ducts than on those milk ducts nearer the free end of a system. In many cases the collateral ducts present many branches. The milk ducts as a whole appear to have a diameter smaller than those of normal animals and the terminal end-buds are not so numerous. Those present, however, stand out very strikingly (Fig. 16).

One hundred and twenty-five days (weight restricted to 10 gm. for twenty days; then placed on normal diet until time of killing. Gross body weight 97 gm.): In this female specimen the ducts show an arborization very similar to that of a normal rat of about the age of puberty. Several individuals subjected to similar treatment and killed at approximately the same age as this animal show the milk ducts in a condition similar to those of this specimen. Therefore, we can conclude that in animals subjected to severe inanition during the first three weeks of life the mammary glands are so retarded that it is not until near the eighteenth week that the glands have attained a development equal to that of normal animals of about 9 weeks. Along with the growth of the milk ducts the nipples have developed so that they, too, have reached a stage similar to that reached in normal animals about the age of puberty.

Similar refeeding experiments have been carried out on male individuals with results very similar to those obtained in females except that the male ducts do not reach such a high stage of development. The ducts are retarded in the male as in the female; on refeeding, however, they apparently only keep pace with the growth of the body of the animal.

DISCUSSION AND CONCLUSIONS

The test rats used in the first part of this paper may be divided into three classes. In the first class we have those animals that were held at birth weight and killed at various intervals up to about 3 weeks of age. In the second class are included animals which were starved from birth but were allowed to reach a weight approximately double that at the time of birth. These animals were killed at various stages, the oldest being 65 days of age. The third stage includes animals starved from birth, but whose body weights were allowed to increase

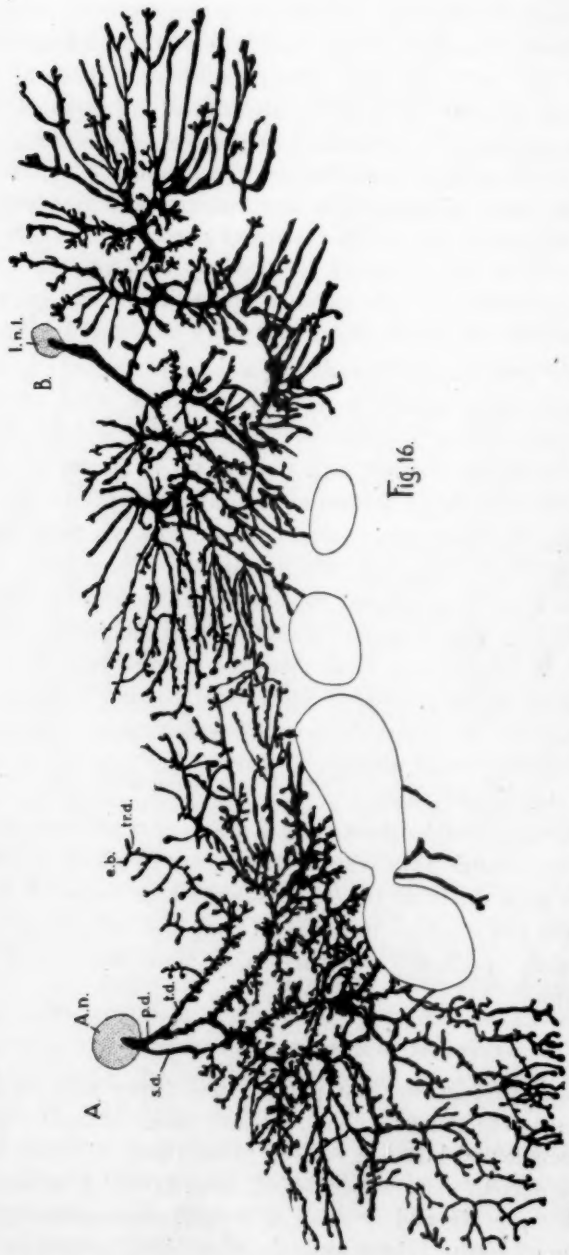

Fig. 16.

Fig. 16.—Same as Figure 15, but animal was placed on normal diet at end of period of starvation until 112 days old, at which time it weighed 85 gm., × 5. Compare this figure with Figures 12 and 13 of an earlier paper (Am. J. Anat. **19**:385, 1916.

to approximately three or four times the birth weight. The oldest animal in this class was underfed for seventy days before killing.

In the first class it was noticed that the milk ducts grew very little during the first week, after which time growth apparently ceases. However, the nipple becomes somewhat more elevated above the surface than normally at the time of birth.

It has been shown (Stewart[6]) that in animals held at birth weight by underfeeding for various periods, the integument increases about 25 per cent. in weight. There is normally a strong tendency for the integument to grow during the first week of life. Jackson and Lowrey[7] and Jackson[8] showed that during this first week of life the integument increases from 20 per cent. to 26 per cent. of the body weight. In Stewart's test animals a fair coat of hair developed. It is therefore possible that the hair and follicles play a considerable rôle in increasing the weight of the integument. As shown in the present article, the mammary glands increase in size but little, however, and therefore scarcely participate in the increase of the weight of the integument during the underfeeding period. Further histologic study of the integument is necessary to ascertain whether parts other than the hair and mammary glands increase in size during this severe inanition.

In the second class, where the body weight in the underfed rats doubled that at the time of birth, the milk ducts show a slight increase, but are not equal to those of a normal animal of the same body weight. These animals are considerably older than those in Class 1, all being killed after the third week. In rats similarly underfed from birth, the body weight being retarded so as to reach only 10 gm. at 3 weeks of age, Stewart[9] found the weight of the integument about equal to that of normal controls of the same body weight. In rats underfed at a later period, beginning at three weeks of age, Jackson[10] has shown that there is a marked loss in the relative weight of the integument.

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6. Stewart, C. A.: Changes in the Weights of the Various Parts, Systems and Organs in Albino Rats Kept at Birth Weight for Various Periods, Am. J. Physiol. **48**:67, 1919.

7. Jackson, C. M., and Lowrey, L. G.: On the Relative Growth of the Component Parts (Head, Trunk and Extremities) and Systems (Skin, Skeleton, Musculature and Viscera) of the Albino Rat, Anat. Rec. **6**:449, 1912.

8. Jackson, C. M.: Postnatal Growth and Variability of the Body of the Various Organs in the Albino Rat, Am. J. Anat. **15**:1, 1913.

9. Stewart, C. A.: Changes in the Relative Weights of the Various Parts, Systems and Organs of Young Albino Rats Underfed for Various Periods, J. Exper. Zool. **25**:301, 1918.

10. Jackson, C. M.: Effects of Acute and Chronic Inanition on the Relative Weights of the Various Organs and Systems of Adult Albino Rats, Am. J. Anat. **118**:75, 1915; Changes in the Relative Weights of the Various Parts, Systems and Organs of Young Albino Rats Held at Constant Body Weights by Underfeeding for Various Periods, J. Exper. Zool. **19**:99, 1915.

The effect of inanition at various ages on the weight of the integument is discussed by Jackson[10] and Stewart.[11] They state that the loss in weight of the integument in young rats during underfeeding is probably due largely to loss of fat.

In a study (uncompleted) on the subcutaneous fat of the albino rat I have been able to demonstrate the presence of considerable amounts of such fat deposit in fairly definite pads in the subcutaneous tissues of the rat before three weeks of age. In the underfed rats used by Jackson and Stewart the fat deposited in the subcutaneous fat depots was of course soon consumed. In my preparations the starving began at the time of birth, but extended far beyond the three week stage. In such rats the body weight increased somewhat during which time the mammary glands showed a very slight increase. No observations have been made to determine whether the mammary glands remain stationary or (like the weight of the integument) actually undergo a decrease in size when the inanition begins at the third week of age or later.

The mammary glands of the rats in the third class (although subjected to less severe inanition) do not show anything essentially different from those of the second class just described. In general, the development of the mammary glands in rats thus stunted by underfeeding is retarded in proportion to the body weight.

It is generally believed that there is such a close relationship existing between the mammary glands and the ovaries that when important changes take place in the ovaries the mammary gland might also be affected. In view of this fact it is interesting to compare the growth of these organs in starved animals. Stewart[6] showed that in animals held at birth weight for sixteen days the ovaries increase about 5 per cent. The mammary glands from these same animals here described under Class 1 show only a very slight increase. Therefore, one may conclude that the two organs undergo a somewhat parallel development under these conditions. In those animals underfed from birth to 3 weeks, body weight 10 gm., and those underfed from birth to 10 weeks, body weight 15 gm., Stewart[9] found the ovaries increased in weight 83 per cent. and 54 per cent., respectively. My Figures 7 and 8 show a much smaller increase in the mammary glands under the same conditions. There is, therefore, apparently no close correlation between the growth of the mammary glands and that of the ovaries in underfed young rats.

As shown by the present study, the mammary glands apparently respond somewhat slowly when the animals are refed after under-

11. Stewart, C. A.: Growth of the Body and of the Various Organs of Young Albino Rats after Inanition for Various Periods, Biol. Bull. **31**:16, 1916.

feeding from birth to about 3 weeks of age. In fact, the response was so delayed that the mammary glands did not reach the stage of development ordinarily attained at the time of puberty (about 8 or 9 weeks) until the refed rat had reached an age of about 18 weeks. Stewart[11] showed that in rats on which the underfeeding was begun at the time of weaning (3 weeks) or later, and underfed for short periods, the integument and ovaries recovered very rapidly when the animals were refed. Later, however, Jackson and Stewart[9] showed that when the underfeeding is begun at birth and continued three weeks or longer, a permanent stunting of the body usually occurs. In view of the great individual variation in the development of the mammary glands at any given age or body weight (as shown by Myers[4]), it is hazardous to draw any final conclusions from the relatively few cases observed in the present study. Apparently, however, the mammary glands in the underfed young rats, though temporarily lagging somewhat behind the body weight when the rats are fully refed, ultimately may attain a normal degree of development.

SUMMARY

1. Severe inanition retards the growth of the milk ducts of the female rat during the first week, but apparently does not completely stop their growth. In animals held at birth weight for a longer time the ducts cease to grow, and remain in a condition slightly more developed than at the time of birth. If after the first week the gross body weight of the animals is allowed to increase so as to correspond with that of a normal animal of one week, the milk ducts fail to develop to the same extent as those of a normal animal of corresponding body weight. This also holds true if the body weight of the underfed rat is allowed to equal that of a normal animal of two weeks.

2. The lumen of the primary duct in underfed rats does not communicate with the exterior through the milk pore until the tenth week.

3. The growth of the milk ducts of male rats is retarded by inanition in a manner similar to that of the female.

4. The nipple grows very little during inanition, being elevated above the surface only slightly in young rats starved severely for eight to ten weeks. The epithelial processes fail to develop much beyond the stage reached at birth, and the sulcus around the base of the normal nipple remains shallow.

5. The subcutaneous fat that appears very early in the neighborhood of the milk ducts soon becomes greatly decreased after the amount of food is reduced to a minimum.

6. In all, the retardation in the development of the mammary gland is roughly proportional to the retardation in body weight (at least within limits of normal variability).

7. Severe inanition for a short time at an early age thus temporarily stunts the mammary glands. When the animal is refed the glands respond slowly. When the body weight during refeeding reaches that of a normal rat at the age of puberty, the milk ducts are far behind those of the normal rat at corresponding body weight. That this stunting is not permanent is shown by the fact that the ducts ultimately attain the same stage of development as those of a normal animal, but at a much later period.

RECOVERY OF NORMAL WEIGHT IN THE VARIOUS ORGANS OF ALBINO RATS ON REFEEDING AFTER UNDERFEEDING FROM BIRTH FOR VARIOUS PERIODS *

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Previous research by ourselves and others (summarized by Jackson and Stewart,[1] 1918) has shown that in young animals underfed for various periods remarkable changes occur in the weights of the various organs and parts of the body. There is also evidence indicating that similar changes occur in malnourished human infants. While some organs during inanition tend to maintain approximately their normal relative weight, and others continue to grow, still others undergo losses. The organs affected and the extent of the changes involved vary according to the age of the individual and the length and character of the inanition.

The question naturally follows as to the process of recovery on abundant refeeding after various periods of inanition. Stewart[2] has already shown that rapid recuperation occurs in rats refed after being held at maintenance (constant body weight) from the age of weaning (3 weeks) to about the age of puberty (10 or 12 weeks). The various organs and parts usually recover their normal relative weights within four weeks of refeeding. The object of the present investigation is to determine the extent of recovery on similar refeeding of rats which have been underfed from birth, during a period in which the changes due to underfeeding are much greater than at later periods (Stewart,[3] 1918, 1919). The results may perhaps indicate the probability of recovery in the various organs of infants after periods of inanition, a clinical problem of obvious importance.

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* From the Institute of Anatomy, University of Minnesota.

1. Jackson, C. M., and Stewart, C. A.: The Effects of Underfeeding and Refeeding on the Growth of the Various Systems and Organs of the Body, Minnesota Med. **1**:403, 1918.

2. Stewart, Chester A.: Growth of the Body and of the Various Organs of Young Albino Rats after Inanition for Various Periods, Biol. Bull. **31**:16, 1916.

3. Stewart, Chester A.: Changes in the Relative Weights of the Various Parts, Systems and Organs of Young Albino Rats Underfed for Various Periods, J. Exper. Zool. **25**:301, 1918. Ibid. Changes in the Weights of the Various Parts, Systems and Organs in Albino Rats Kept at Birthweight for Various Periods, Am. J. Physiol. **48**:67, 1919.

MATERIAL AND METHODS

The albino rat (*Mus norvegicus albinus*) was used as heretofore, including complete data for 31 test rats (15 males, 16 females) and 22 controls (9 males, 13 females), the individuals being listed in Table 1. For intestinal lengths, 45 additional test rats (26 males, 19 females) and 24 controls (12 males, 12 females) were used, corresponding chiefly to the same individuals used in previous papers by Stewart[3] (1918 and 1919). The letters "St" (Stewart) refer to the series, the number preceding the decimal point refers to the litter and the number following designates the individual rat. Thus, it is apparent that, for the most part, the test rats and controls were from the same litters. This is a matter of importance, especially in view of the comparatively small number of animals used, since it has been shown by Jackson[4] and King[5] that variability in weight within the litter is very much less than that of the rat population in general.

The rats were well cared for in the animal rooms of the Institute of Anatomy, and were kept as nearly as possible under uniform environment, varying only the nutritive conditions as desired. The necropsies were performed and the data carefully recorded by Stewart, the technic being the same as that described in our previous articles.

The test rats were all underfed by removal from the mother for various successive periods from birth up to the period of weaning (about three weeks), and later by feeding restricted amounts of whole wheat (Graham) bread, soaked in whole milk. Water (city supply, from Mississippi river) was also furnished. Some of the rats were underfed from birth to 3 weeks of age. The gross body weight during this time increased from about 5 gm. to only about 10 gm., whereas normally it would have increased to 20 or 25 gm. Some were similarly underfed from birth to 6 weeks (exact average being 45 days), reaching an average weight of 13 to 14 gm. (normal at this time being about 50 gm). In some, the underfeeding was prolonged from birth to the age of 10 weeks (66 days in group E, 67 days in group F) the body weight reaching about 16 gm. (normal about 100 to 120 gm.). These three groups were therefore in the same condition as those in which Stewart[3] (1918) has determined the changes in the weights of the organs and parts at the end of the underfeeding period.

The first group (underfed from birth to 3 weeks), shown in Tables 1 and 2, were then placed on a full diet of bread and milk, and refed until they had reached body weights of approximately 25 gm., 50 gm. or 75 gm., respectively. The second group (underfed to 6 weeks) were similarly refed until they had reached a body weight of about 75 gm. The third group (underfed to 10 weeks) were similarly refed, some to about 50 gm. and the others to about 75 gm., as shown in Tables 1 and 2.

The normal controls were likewise killed in three groups, with approximate gross body weights of 25, 50 and 75 gm., respectively, corresponding to the *final* body weights of the various test groups.

It is thus possible to compare directly the weights of organs in the controls and in the test groups, and to ascertain in each case to what extent they approach the normal for corresponding body weight. The difference is expressed in Table 2 as a *percentage* (plus or minus) in each case. The correction for differences in body weight between control and test groups is so slight that it was ignored. There is also

4. Jackson, C. M.: Postnatal Growth and Variability of the Body and of the Various Organs in the Albino Rat, Am. J. Anat. **15**:1, 1913.

5. King, Helen D.: The Growth and Variability in Body Weight of the Albino Rat, Anat. Rec. **9**:751, 1915.

TABLE 1.—Albino Rats Used. Individual Data for Sex, Age, Gross Body Weight and Body Length

	Rat Number	Sex	Age, Days	Gross Body Weight, Gm.	Nose-Anus Length, Mm.
Normal controls	St 95.4	M	20	24.4	88
	St 104.6	M	23	26.2	90
	St 131.1	M	22	26.4	89
	St 157.6	M	22	29.6	98
	St 98.1	F	21	22.4	87
	St 104.5	F	23	26.5	90
	St 106.3	F	20	25.5	91
	St 132.5	F	20	28.0	93
	Average.....	.....	21.4	26.1	90.8
Underfed from birth to 3 weeks and refed	St 106.2	M	35	25.0	98
	St 131.2	M	29	27.2	96
	St 131.4	M	29	25.0	95
	St 150.4	M	32	25.0	93
	St 106.1	F	33	25.6	95
	St 128.1	F	33	26.5	97
	St 132.3	F	34	25.3	96
	St 132.6	F	34	27.5	98
	St 150.1	F	32	25.6	95
	Average.....	.....	32.3	25.9	95.9
Normal controls	St 154.2	M	42	55.4	126
	St 107.6	M	35	50.5	121
	St 109.4	M	37	52.8	120
	St 167.2	M	30	51.5	119
	St 153.1	F	48	49.5	119
	St 153.6	F	37	44.5	116
	St 171.3	F	27	49.0	118
	St 154.5	F	45	56.5	121
	St 152.1	F	43	50.0	124
	Average.....	.....	38.2	51.1	120.4
Underfed from birth to 3 weeks and refed	St 144.5	M	51	49.6	130
	St 144.6	M	51	49.5	123
	St 152.4	M	51	52.0	120
	St 144.1	F	54	53.3	126
	St 144.2	F	59	53.5	123
	St 144.4	F	48	50.0	124
	St 152.3	F	52	51.5	122
	St 152.7	F	51	50.0	117
	St 152.9	F	49	50.0	120
	Average.....	.....	51.6	51.0	122.8
Underfed from birth to 66 days and refed	St 158.8	F	77	46.9	119
	St 154.7	F	82	51.7	121
	St 159.3	F	82	52.0	128
	St 153.10	F	81	51.1	123
	Average.....	.....	80.5	51.7	122.8
Normal controls	St 91.9	M	48	76.0	141
	St 143.3	M	46	77.0	140
	St 155.2	F	53	73.0	137
	St 168.1	F	50	75.5	140
	St 170.1	F	46	80.3	135
	Average.....	.....	48.6	76.4	138.6
Underfed from birth to 3 weeks and refed	St 137.4	M	61	76.6	141
	St 137.6	M	61	75.5	136
	St 143.1	M	54	75.5	140
	St 143.9	M	56	78.5	145
	St 147.1	M	67	77.0	140
	St 147.4	F	94	74.8	141
	Average.....	.....	65.5	76.3	140.5
Underfed from birth to 45 days and refed	St 91.4	M	89	80.5	135
	St 91.8	M	96	74.0	133
	Average.....	.....	92.5	77.3	134.0
Underfed from birth to 67 days and refed	St 154.3	F	101	75.5	139.0

TABLE 2.—Data for Various Parts and Organs; Averages for Groups of Rats, According to Tests, with Corresponding Normal Controls and Percentage Difference

Description	A. Underfed from Birth to 3 Weeks of Age and Refed to about 25 Gm. (with Controls)			B. Underfed from Birth to 3 Weeks of Age and Refed to about 50 Gm. (with Controls)			C. Underfed from Birth to 3 Weeks of Age and Refed to about 75 Gm. (with Controls)			D. Underfed from Birth to 6 Weeks (45 days) of Age and Refed to about 75 Gm. (with Controls)			E. Underfed from Birth to 10 Weeks (66 days) of Age and Refed to about 50 Gm. (with Controls)			F. Underfed from Birth to 10 Weeks (67 days) of Age and Refed to about 75 Gm. (with Controls)		
	Controls	Test Rats	Difference	Controls	Test Rats	Difference	Controls	Test Rats	Difference	Controls	Test Rats	Difference	Controls	Test Rats	Difference	Controls	Test Rats	Difference
Number and sex	4M, 4F	4M, 5F	.....	4M, 5F	3M, 6F	.....	2M, 3F	5M, 1F	.....	2M	2M	.....	5F	4F	.....	3F	1F	
Age, days	21.4	32.3	.....	38.2	51.6	.....	48.6	65.5	.....	47.0	92.5	.....	40.0	80.5	.....	49.7	101.0	
Body weight, Gm.:																		
Gross	26.1	25.9	−0.8	51.1	51.0	−0.2	76.4	76.3	−0.1	76.5	77.3	+1.0	45.7	47.9	+4.8	69.2	71.2	+2.9
Net	24.2	24.1	−0.4	47.2	47.5	+0.6	70.1	71.6	+2.1	72.0	71.3	−0.1	49.9	51.7	+3.6	76.3	75.5	−0.1
Nose-anus lenth, Mm.	90.8	95.9	+6.0	120.4	122.8	+2.0	138.6	140.5	+1.4	140.5	134.0	−4.6	119.6	122.8	+2.7	137.3	139.0	+1.2
Tail lenth, Mm.	60.0	63.0	+5.0	95.3	96.7	+1.5	116.0	109.0	−6.0	111.0	113.0	+1.8	96.0	90.0	−6.3	118.0	111.0	−5.9
Head, Gm.	4.84	4.56	−5.8	6.89	6.50	−5.7	8.68	8.70	0.0	8.75	8.75	0.0	6.80	6.43	−5.4	8.63	8.40	−2.7
Fore limbs, Gm.	1.79	1.87	+4.5	3.54	3.29	−7.1	4.96	5.17	+3.8	4.97	4.71	−5.6	3.45	3.45	0.0	4.95	5.61	+13.3
Hind limbs, Gm.	3.39	3.56	+5.0	7.54	7.57	+0.4	11.50	11.73	+2.0	11.61	11.18	−3.7	7.40	7.06	−4.3	11.43	10.62	−7.1
Trunk, Gm.	14.17	14.14	−0.2	29.00	30.16	+4.0	45.20	46.51	+2.9	46.67	46.63	0.0	27.67	30.92	+11.8	44.23	46.55	+5.2
Integument, Gm.	4.89	3.91	−20.1	8.81	8.49	−3.6	13.36	13.75	+2.9	14.06	14.65	+4.2	8.37	9.21	+10.0	12.90	17.06	+32.3
Skeleton:																		
Ligament, Gm.	3.77	4.04	+7.2	6.34	5.91	−6.8	7.98	8.24	+3.3	8.46	7.89	−6.7	6.15	5.76	−6.3	7.66	8.07	+5.4
Moist cartilage, Gm.	3.04	2.87	−5.6	5.51	5.00	−9.3	7.20	7.06	−1.9	7.19	5.80	−19.3	5.39	3.97	−26.3	7.23	7.75	+7.2
Dry cartilage, Gm.	0.768	0.790	+2.9	1.80	1.59	−11.7	2.56	2.41	−5.9	2.51	1.81	−27.9	1.89	.....	.....	2.68		
Musculature, Gm.	6.98	7.31	+4.7	16.12	15.94	−1.1	26.84	27.71	+3.2	28.08	26.47	−5.7	15.79	13.36	−15.4	26.01	24.05	−7.5
Visceral group, Gm.	5.39	5.51	+2.2	8.88	9.32	+5.0	12.71	12.25	−3.6	13.68	12.04	−12.0	8.84	9.90	+12.0	12.07	13.12	+8.7
Remainder, Gm.	3.18	3.24	+1.9	7.05	7.93	+12.5	9.42	9.65	+2.4	7.67	10.22	+33.2	6.59	10.39	+57.6	10.59	8.89	−16.0
Brain, Gm.	1.331	1.162	−12.7	1.496	1.252	−16.3	1.488	1.314	−11.7	1.500	1.437	−4.2	1.446	1.120	−22.5	1.479	1.244	−15.9
Spinal cord, Gm.	0.184	0.194	+5.4	0.279	0.261	−6.5	0.317	0.311	−1.3	0.323	0.321	−0.6	0.268	0.248	−7.5	0.313	0.278	−11.2
Eyeballs, Gm.	0.117	0.128	+9.5	0.161	0.158	−1.9	0.177	0.179	+1.1	0.173	0.206	+19.1	0.161	0.170	+5.6	0.179	0.194	+8.4
Hyphophysis, Gm.	0.0024	0.0024	0.0	0.0031	0.0028	−10.0	0.0044	0.0039	−11.4	0.0042	0.0048	+14.3	0.0030	0.0034	+13.3	0.0046	0.0041	−10.9
Pineal body, Gm.	0.00100	0.00094	−6.0	0.00114	0.00102	−10.5	0.00108	0.00102	−5.6	0.00110	0.00115	+4.6	0.00118	0.00098	−17.0	0.00107	0.00080	−25.2
Thyroid Gland, Gm.	0.0074	0.0064	−13.5	0.0090	0.0076	−15.6	0.0111	0.0117	+7.2	0.0142	0.0149	+4.9	0.0076	0.0073	−4.0	0.0091	0.0097	+6.6
Thymus, Gm.	0.079	0.076	−3.8	0.152	0.174	+14.5	0.263	0.233	−11.4	0.275	0.201	−26.9	0.131	0.109	−16.8	0.256	0.260	+1.6
Heart, Gm.	0.181	0.177	−2.2	0.285	0.268	−6.0	0.374	0.373	0.0	0.380	0.385	+1.3	0.264	0.315	+19.3	0.370	0.421	+13.8
Lungs, Gm.	0.277	0.281	+1.4	0.406	0.355	−12.6	0.482	0.489	+1.5	0.475	0.494	+4.0	0.363	0.429	+18.2	0.485	0.635	+30.9
Liver, Gm.	1.36	1.35	−0.7	2.41	2.79	+15.8	4.16	3.75	−9.9	4.19	4.18	−0.2	2.51	2.96	+17.9	4.14	3.84	−7.3
Spleen, Gm.	0.094	0.143	+52.1	0.219	0.293	+33.8	0.452	0.450	0.0	0.337	0.255	−24.3	0.236	0.500	+112.0	0.528	0.468	−11.4
Stomach and Intestines:																		
With contents, Gm.	3.24	3.32	+2.5	6.57	6.58	+0.1	9.75	8.47	−13.1	8.60	9.10	+5.8	7.07	7.24	+2.4	10.52	9.16	−13.0
Empty, Gm.	1.31	1.58	+20.6	2.68	3.05	+13.8	3.71	3.75	+1.1	4.04	3.11	+23.0	2.89	3.40	+17.7	3.49	4.83	+38.4
Suprarenals, Gm.	0.0091	0.0093	+2.2	0.0148	0.0137	−7.4	0.0180	0.0178	−1.1	0.0172	0.0190	+10.5	0.0143	0.0144	+0.7	0.0185	0.0215	+16.2
Kidneys, Gm.	0.347	0.335	−3.5	0.561	0.511	−8.9	0.792	0.736	−7.0	0.804	0.801	−0.4	0.530	0.625	+17.9	0.784	0.899	+14.7
Testes, Gm.	0.120	0.141	+17.5	0.375	0.447	+19.2	1.047	0.579	−44.6	1.047	0.528	−49.4						
Epididymides, Gm.	0.025	0.026	+4.0	0.055	0.056	+1.8	0.108	0.079	−26.9	0.108	0.090	−16.7						
Ovaries, Gm.	0.0094	0.0115	+22.3	0.0108	0.0104	−3.7	0.0140	0.0162	+15.8	.....	.....	.....	0.0108	0.0086	−20.4	0.0140	0.0100	−28.6

a slight error involved in computing the percentages from the *average* for the group, rather than for each individual separately. Finally, of course, due allowance must be made for experimental error and normal variability, in view of the comparatively small number of observations in each group. These considerations make it necessary to be cautious in drawing final conclusions, although the results in general seem to justify some provisional conclusions, as will appear later.

If the data for the normal control rats in the present series are compared with the normal tables of Donaldson,[6] derived from the formulas of Hatai,[7] a general agreement is found, although certain differences appear. As we have repeatedly noted, in the normal rats from the Minnesota and Missouri colonies, the weight of the liver is constantly lower, and that of the spleen higher, than the Wistar norm for rats of the same body length or weight (Jackson,[4] Stewart,[2, 3] 1916 and 1918). In the present series, the body length in the normal rats averages slightly below the Wistar norm for animals of the same body weight, that is, our animals are relatively a little heavier for the same body length. The tails are likewise somewhat shorter in our series. The thymus is heavier than the Wistar norm for the corresponding age, usually also for the corresponding body weight. The empty stomach and intestines are lighter, and the ovaries somewhat heavier, than the Wistar norm. In the other organs, there is but slight or inconstant difference. It is uncertain whether the above differences mentioned are accidental (due to chance variation in the small series), environmental (due to differences in diet, temperature, etc.), or germinal (due to different varieties or strains of albino rats). At any rate, they emphasize the necessity of having direct controls in experimental work of this kind. The Wistar norm is, of course, also exceedingly valuable as a common standard, whereby variations in local strains may be recognized and compared.

In Table 1, the individual (gross) body weights and body lengths are given, which will show the variations within each group. For economy of space, only the averages are given in each group for the other data (Tables 2 and 3). The normal variability and correlation in the weight of the various organs has been studied by Jackson.[4] The individual data in the present series, as heretofore, will be deposited in the Wistar Institute of Anatomy, Philadelphia, where they will be available to those interested.

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6. Donaldson, H. H.: The Rat. Reference Tables and Data for the Albino Rat and the Norway Rat, Memoirs Wistar Inst. Anat. and Biol. 1915, No. 6.

7. Hatai, S.: On the Weights of the Abdominal and Thoracic Viscera, the Sex Glands, Ductless Glands and the Eyeballs of the Albino Rat (*Mus norvegicus albinus*) According to body weight, Am. J. Anat. **15**:87, 1913.

TABLE 3.—AVERAGE LENGTH OF LARGE AND SMALL INTESTINES IN THE VARIOUS GROUPS OF ALBINO RATS *

	Age, Days	Number and Sex	Gross Body, Weight, Gm.	Body Length, Mm.	Length of Intestine		Ratio of Intestine to Body Length	Ratio of Small to Large Intestine
					Large, Mm.	Small, Mm.		
A. Normal controls	1	1 M, 1 F	4.3	46(est.)	20.0	179	4.3	9.0
	9	6 M, 6 F	10.0	63	41.8	307	5.5	7.4
	13	3 M, 3 F	15.5	74	45.7	355	5.4	7.8
	21	3 M, 5 F	25.8	90	66.3	501	6.3	7.6
	39	3 M, 4 F	50.9	121	99.9	682	6.5	7.8
	49	2 M, 3 F	76.4	139	117.0	892	7.3	7.6
B. Underfed from birth to age indicated	19	2 M, 2 F	5.0	56.0 (+22)	36.2 (+81)	239 (+25)	4.9	6.6
	22	15 M, 9 F	10.1	68.0 (+8)	48.3 (+15)	349 (+14)	5.8	7.2
	42	4 M, 3 F	13.7	79.3	64.3	506	7.2	7.9
	67	7 M, 4 F	15.3	85.3 (+15)	67.3 (+47)	553 (+56)	7.3	8.2
C. Refed after underfeeding from birth to 3 weeks of age	33	4 M, 5 F	25.9	96.0 (+6)	76.4 (+15)	560 (+12)	6.6	7.3
	52	3 M, 5 F	50.8	122.4 (+1)	97.0 (—3)	745 (+9)	6.9	7.7
	66	5 M, 1 F	76.3	140.5 (+1)	105.3 (—10)	832 (—7)	6.7	7.9
D. Refed after underfeeding from birth to 6 weeks of age	93	2 M	77.3	134 (—4)	122.5 (+5)	877 (—2)	7.5	7.2
E. Refed after underfeeding from birth to 10 weeks of age	81	4 F	51.9	123 (+2)	107.3 (+7)	802 (+18)	7.4	7.5
	101	1 F	75.5	139 (+0)	114.0 (—3)	798 (—10)	6.6	7.0

* Figures in parenthesis indicate percentage changes of corresponding part, in comparison with normal controls of nearly the same body weight.

Body Weight. — The average time required to reach the body weights of 25, 50 and 75 gm. on refeeding in the various groups may be learned from the data in Table 2. Thus, Group A, underfed from birth to three weeks, required an average of 11.3 days (final age 32.3 days) of ample refeeding to reach a body weight of about 25 gm. Similarly to reach about 50 (51) gm. (Group B) required 30.6 days, and to reach 75 (76.3) gm. (Group C) required 44.5 days of refeeding.

In Group D, underfed from birth to about 6 weeks (45 days), 47.5 days of ample refeeding were required to reach a final body weight of about 75 (77.3) gm.

In Group E, underfed from birth to about 10 weeks (66 days), only 14.5 days of ample refeeding were required to reach a body weight of 50 gm. This is astonishingly rapid growth, in comparison with the time required for Group B to reach the same body weight. In Group F, similarly underfed to ten weeks (67 days), only 34 days of refeeding were required to reach a body weight of 75 gm. This is likewise a shorter time than that required to reach the same body weight by Groups C and D, which had been underfed for shorter periods.

This more rapid recovery of body weight in the groups underfed to ten weeks of age is in part explained by the fact that they had reached a somewhat higher body weight at the end of the underfeeding period. Some time would naturally be required on refeeding

to enable the rats at 10 or 13 gm. body weight to reach the initial weight of about 16 gm. which had been attained by Groups E and F at the end of the underfeeding period.

But this difference in initial body weight is insufficient to explain the shorter time of refeeding required for Groups E and F. Even when all due allowance is made, the surprising fact remains that the recovery in body weight after the longer underfeeding period is more rapid than after the shorter underfeeding periods. This, of course, might be due to an accidental variation, as individuals differ considerably in their resistance to inanition and in power of recuperation. That it is not merely an accidental variation, however, is indicated by the somewhat similar results of Stewart,[2] who found that rats amply refed after maintenance by underfeeding from 3 to 6, 8 or 10 weeks of age actually grow more rapidly than normally, so as to overtake later the normal controls of the same age. In Stewart's series it also appears that for a time the growth on refeeding was slightly more rapid in the groups (especially the females) underfed to 10 weeks (compare his Charts A and B). This surprising phenomenon of more rapid growth on refeeding does not necessarily mean that those underfed for the longer periods will ultimately reach full normal body weight, although this apparently happened in most of Stewart's earlier series (Jackson and Stewart[1]). It furthermore does not necessarily mean that the various organs and parts of the body have more quickly regained their normal proportions in the groups refed after the longer underfeeding periods. As will be shown later, this is frequently not the case.

The phenomenon of unusually rapid growth following periods of growth suppression has previously been noted by Hatai,[8] Ferry,[9] and Osborne and Mendel[10] in the rat, as well as in other animals (see citations by Stewart[2]). A similar phenomenon has likewise been noted in children by Coudereau,[11] Pagliani,[12] Schloss,[13] Boas[14] and others.

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8. Hatai, S.: Effect of Partial Starvation, Followed by a Return to Normal Diet, on the Growth of the Body and Central Nervous System of Albino Rats, Am. J. Physiol. **18**:309, 1907.

9. Ferry, Edna L.: The Rate of Growth of the Albino Rat, Anat. Rec. **7**: 1913, No. 12.

10. Osborne, T. B., and Mendel, L. B.: The Resumption of Growth after Long-Continued Failure to Grow, J. Biol. Chem. **23**: 1915. Ibid. Acceleration of Growth after Retardation, Am. J. Physiol. **40**: No. 1, 1916.

11. Coudereau: Récherches chimiques et physiologiques sur l'alimentation des enfants, Paris, 1869. (Cited by Hatai, Footnote 8.)

12. Pagliani: Giornale della reale Società italiana d'igiene, Milano **1**: 1879. (Cited by Hatai, Footnote 8.)

13. Schloss, E.: Die Pathologie des Wachstums im Säuglingsalter, Berlin, 1911.

14. Boas, F.: The Growth of Children, Science, New Series **36**:815, 1912.

Body Length and Tail Length.—The body length is measured from the tip of the nose to the anus, the trunk being slightly extended. Stewart[3] (1918) found that in rats underfed from birth (to the same extent as those of the present series) the body length had increased in the test rats, as compared with normal controls of the same body weight. The increase amounted to 6 per cent. in those underfed to the age of 3 weeks, 9 per cent. in those underfed to 6 weeks, and 13 per cent. in those underfed to 10 weeks.

As shown by the data in Table 2, the rats of the present series on ample refeeding after the various inanition periods rapidly regain their normal weight-length proportions. In those underfed from birth to 3 weeks of age (body weight about 10 gm.) and refed to a body weight of 25 gm., the body (nose-anus) length has apparently not yet reached its normal ratio, however, being still 6 per cent. greater than in the normal controls. Rats of the same group refed to body weights of 50 and 75 gm. show normal lengths, however, the difference of 2 per cent. being doubtless within the range of normal variation. The differences in the groups refed after underfeeding to 6 and 10 weeks are probably likewise of no significance.

The tail was found by Stewart[3] (1918) to become relatively elongated in rats underfed from birth to 3, 6 or 10 weeks of age. His data show an average increase of about 44 per cent., 38 per cent., and 61 per cent., respectively, as compared with normal controls of the same body weight.

As is evident from our Table 2, such rats, on ample refeeding to a body weight of 25 gm. or more, rapidly recover the normal tail ratio. The plus or minus differences do not exceed 5 or 6 per cent., and are probably within the range of normal variation. Although there is a difference in tail length according to sex (the tail in the female being slightly longer), a grouping of the data according to sex leads to the same conclusion as to recovery of the normal tail length. The sexes are, therefore, combined in the table.

A similar elongation of the body and tail was observed in rats held at maintenance (constant body weight), beginning at 3 weeks of age, by Jackson,[15] who noted that the tail normally undergoes relative elongation in the growing young rats at this period. Stewart[2] found that the abnormal body length and tail ratio in rats held at maintenance from the age of 3 to 12 weeks disappears rapidly on

15. Jackson, C. M.: Changes in the Relative Weights of the Various Parts, Systems and Organs of Young Albino Rats Held at Constant Body Weight by Underfeeding for Various Periods, J. Exper. Zool. **19**:99, 1915.

ample refeeding, the normal proportions usually being regained within one week.

Head, Limbs and Trunk.—In rats underfed from birth to 3 weeks of age, Stewart[3] (1918) found a relative increase of about 16 per cent. in the weight of the head, in comparison with normal controls of the same body weight. In those underfed to 6 or 10 weeks of age, however, the head was nearly normal, the difference not exceeding 4 per cent.

The data from the present series (Table 2) indicate that such rats on refeeding to 25 gm. body weight, or more, rapidly regain their normal relative head weight. It is doubtful whether the slight underweight (—5.8 and —5.7 per cent.) of the head in the first two groups has any special significance.

Jackson[15] found little if any increase in head weight in rats held at maintenance from age of 3 to 10 weeks, and Stewart[2] found nearly normal head weight in such rats throughout the period of refeeding.

Although there is considerable change in the normal proportions of the limbs and trunk of the rat during the postnatal growth period (Jackson and Lowrey[16]), there appears to be no marked or constant change in their relative weight in the young during various periods of underfeeding and refeeding (Jackson,[15] Stewart,[2, 3] 1916, 1918). Likewise, in the present experiments, as shown by Table 2, the proportions of the forelimbs, hindlimbs and trunk remain nearly normal. The apparent differences are comparatively small, and are probably due chiefly to normal variability and experimental error. Allowance must be made for the difficulty in removing the limbs in a uniform manner.

The Integument.—In rats underfed from birth, Stewart[3] (1918) found no appreciable change in the relative weight of the integument at 3 weeks of age, though at 6 and 10 weeks there was a loss of 43 to 48 per cent., compared with normal controls of the same body weight.

In the present series, assuming that the integument was likewise normal in weight in the rats underfed from birth to 3 weeks, it is difficult to account for the apparent loss of 20.1 per cent. on ample refeeding to a body weight of 25 gm. (Table 2, A). In the succeeding groups, the recovery of normal relative weight is apparent. In the rat refed to 75 gm. after underfeeding from birth to 10 weeks (Table 2, F), there is even an apparent overgrowth of the integument (+32.3

16. Jackson, C. M., and Lowrey, L. G.: On the Relative Growth of the Component Parts (Head, Trunk and Extremities) and Systems (Skin, Skeleton, Musculature and Viscera) of the Albino Rat, Anat. Rec. **6**:449, 1912.

per cent.), although this may be merely an accidental variation. It is difficult to remove the integument in a uniform manner, due to the underlying subcutaneous layer and dermal sheet of musculature.

In rats underfed at later periods, beginning at three weeks of age, Jackson[15] found losses of 36 per cent. or more in the integument; and Stewart[2] found that in such rats the integument recovered its normal relative weight after two weeks or more of ample refeeding.

Skeleton.—The term "ligamentous skeleton" is used to designate the fresh skeleton together with the attached cartilages, periosteum and ligaments. The "cartilaginous skeleton" was prepared by immersion of the ligamentous skeleton for about one hour in 1 per cent. aqueous "Gold Dust" solution (a soap mixture) at about 95 C., so as to remove all the fibrous tissues. The cartilaginous skeleton, after rinsing in clean water, was first weighed in the moist condition. Then it was dried for several days in an oven at about 85 C., to constant weight.

As shown by the data of Stewart[3] (1918), in rats underfed from birth the skeleton shows a remarkable persistence of growth. In the ligamentous skeleton, the relative increase at 3, 6 and 10 weeks (compared with normal controls of the same body weight) is 19, 13 and 24 per cent., respectively. In the moist cartilaginous skeleton, the increase is much greater, amounting to 94, 33 and 54 per cent., respectively, at the same periods. In the dry skeleton, the corresponding increases reach the astonishing figures of 166, 46 and 100 per cent. Thus the growth of the skeleton during inanition was accompanied by a great increase in the amount of dry substance, together with other indications of the normal process of skeletal development.

The present data (Table 2) show that on ample refeeding to body weights of from 25 to 75 gm. after such periods of underfeeding, the skeleton in general rapidly recovers its normal proportions. Excepting the first group, the ligamentous skeleton in all cases has nearly normal relative weight. The cartilaginous skeleton, both moist and dry, even shows a definite tendency to lag behind that in normal controls of the same body weight, especially in those underfed to 6 and 10 weeks (excepting the female refed to 75 gm.). The data are not conclusive, as there is some difficulty in securing uniformity of technic in the removal of the skeleton, but they suggest the possibility that the early inanition period, while not preventing the *immediate* growth of the skeleton, may produce an effect which tends to inhibit the skeletal growth at later periods, even on ample refeeding.

Persistent increase in length, indicating continued growth of the skeleton in malnourished human infants and children, has been noted

by Variot,[17] Freund,[18] Birk[19] and Hess.[20] A similar persistent skeletal growth during inanition in young animals was observed in calves by Waters[21] (1908), and by Aron[22] in puppies. The first extensive and detailed study of the matter was by Jackson,[15] who found a marked increase in the skeletons of albino rats held at maintenance by underfeeding from 3 to 10 weeks of age. Stewart[2] found that in such rats, on ample refeeding, the skeleton recovers its normal relative weight within two weeks.

Musculature.—In young rats underfed from birth to the age of 3, 6 or 10 weeks, Stewart[3] (1918) found only a slight increase of from 8 to 12 per cent. in the weight of the musculature, compared with normal controls of the same body weight.

The present data (Table 2) indicate that this slight disproportion in the musculature of such rats has disappeared on ample refeeding to 25 gm. or more of body weight. In those refed after underfeeding to 6 and 10 weeks there is, on the contrary, a slight deficit (—5.7 to —15.4 per cent.) in the weight of the musculature. This deficit is of somewhat doubtful significance, but may indicate that the earlier inanition period has a retarding effect on the later growth of the musculature.

In rats held at maintenance by underfeeding from 3 to 10 weeks of age, Jackson[15] found but a very slight increase (3 per cent.) in the weight of the musculature; and Stewart[2] found the musculature of such rats nearly normal in weight after one week of ample refeeding.

Visceral Group and "Remainder."—The visceral group includes all of the individual organs listed in Table 2. As shown by Stewart[3] (1918) the weight of the combined visceral group increases relatively in young rats underfed from birth to 3, 6 or 10 weeks, the increase being 28, 29 and 38 per cent., respectively.

The present data (Table 2) show that in general this excess weight of the visceral group has disappeared in such rats when amply refed

17. Variot, G.: La dissociation de la croissance dans l'atrophie et l'hypotrophie infantiles; atrophie ponderale, atrophie staturale, Bull. et mém. Soc. méd. d. hôp. de Paris, **24**:1347, 1907. Also in Bull. Soc. de pédiat. de Paris **9**:363, 1907.

18. Freund, W.: Zur Pathologie des Längenwachstums bei Säuglingen und über das Wachstum debiler Kinder, Jahrb. f. Kinderh. **70**:752, 1909.

19. Birk, W.: Unterernährung und Längenwachstum beim neugeborenen Kinde, Berl. klin. Wchnschr., J. 48 **2**:1227, 1911.

20. Hess, Alfred F.: Infantile Scurvy. III. Its Influence on Growth (Length and Weight), Am. J. Dis. Child. **12**:152, 1916.

21. Waters, H. J.: The Capacity of Animals to Grow Under Adverse Conditions, Proc. 29th Ann. Meeting, Soc. for Promotion of Agric. Sc. 1908, 71-96. Ibid. The Influence of Nutrition on Animal Form, Presented at the Thirtieth Meeting of the Society for the Promotion of Agricultural Science, 1909.

22. Aron, Hans: Nutrition and Growth, I, Philippine J. Sc., B. **6**:1, 1911.

to 25, 50 and 75 gm. in body weight. The differences are probably due chiefly to accidental variation. There are, however, differences among the various individual organs, which will be considered later. It should be remembered that the weight of the visceral group is dominated largely by the weight of a few larger organs, such as the brain and alimentary tract.

In rats held at maintenance by underfeeding, beginning at the age of 3 weeks, Jackson[15] found in the visceral group a definite increase at 6 and 8 weeks, less marked at 10 weeks. On amply refeeding such rats, Stewart[2] found that the visceral group recovered normal relative weight within a week.

The "remainder" is obtained by subtracting the weight of the integument, ligamentous skeleton, musculature and viscera from the net body weight (intestinal contents excluded). This "remainder" includes various small, unweighed organs, dissectable fat, body fluids, and loss by evaporation, etc. In rats underfed from birth, Stewart[3] (1918) found a very marked loss in the weight of the remainder at 3 weeks (—40 per cent.), with smaller losses at 6 and 10 weeks (—19 and —23 per cent.).

The present data (Table 2) show that in such rats the loss in the "remainder" has been more than fully recovered on ample refeeding to a body weight of 25 gm. or more, excepting the one female underfed to 10 weeks and refed to 75 gm. The considerable excess in Groups D and E is of uncertain significance, since the "remainder" is notably variable.

In rats held at maintenance by underfeeding from 3 to 6, 8 or 10 weeks of age, Jackson[15] found but little change in the weight of the "remainder"; and Stewart[2] found it about normal after various periods of refeeding.

Brain.—In rats underfed from birth to 3 weeks, Stewart[3] (1918) found a remarkable increase in the weight of the brain, the average (sexes combined), amounting to 60 per cent. gain in comparison with normal controls of the same bodyweight. In rats with continued underfeeding to 6 or 10 weeks of age, the excess in brain weight was much less, being 3 and 8 per cent., respectively.

In contrast with this overweight of the brain in the underfed rats, the present data (Table 2) show a uniform underweight of the brain in rats similarly underfed and subsequently amply refed to a body-weight of from 25 to 75 gm. In Group D the deficit is small (—4.2 per cent.), but in the other five groups it is considerable (—11.7 to —22.5 per cent.). This indicates clearly that in spite of the persistent growth of the brain during the earlier underfeeding period, it has been in some way affected by the inanition, so that its later growth

on ample refeeding is somewhat retarded, at least within the period of the present experiments.

Hatai[23] noted an apparent decrease of 4 or 5 per cent. in the weight of the brain in malnourished young rats with protein-poor diet. In a series similarly underfed and then placed on full normal diet, Hatai[8] found later full recovery in the weight of the body and central nervous system. In another underfed series[24] the brain weight apparently remained normal. Donaldson[25] observed a slight increase of the brain weight in rats held nearly at maintenance by underfeeding from 30 to 51 days of age. Jackson[14] found the brain weight nearly constant in rats held at maintenance by underfeeding from 3 weeks of age for various periods, and Stewart[2] found the brain weight normal (in proportion to body weight) in such rats on ample refeeding for various periods.

In a more recent investigation, Stewart[26] found an excess of 33 per cent. in the brain weight of rats underfed from birth to 3 weeks of age (body weight 10 gm.) and of 30 per cent. in those underfed to 8 weeks (body weight 12 gm.). In another series starved more severely so as to hold them at birth weight for an average of 16 days, a remarkable increase of 114 per cent. in the brain weight was found. Stewart further demonstrated that during its growth in these underfeeding periods the brain shows normal growth in the relative weight of its various parts (excepting perhaps the olfactory bulb).

Variot and Lassablière[27] likewise found the growth of the brain in malnourished human infants to be retarded less than the increase in body weight, the brain thus increasing at the expense of other parts of the body.

Spinal Cord.—In rats underfed from birth, Stewart[3] (1918) found (in comparison with normal controls of the same body weight) a relative increase of 70 per cent. in the weight of the spinal cord at 3 and 10 weeks of age, and of 38 per cent. at six weeks.

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23. Hatai, S.: The Effect of Partial Starvation on the Brain of the White Rat, Am. J. Physiol. **12**:116, 1904.

24. Hatai, S.: Preliminary Note on the Size and Condition of the Central Nervous System in Albino Rats Experimentally Stunted, J. Compar. Neurol. and Psychol. **18**:151, 1908.

25. Donaldson, H. H.: The Effect of Underfeeding on the Percentage of Water, on the Ether-Alcohol Extract, and on the Medullation in the Central Nervous System of the Albino Rat, J. compar. neurol. **21**:139, 1911.

26. Stewart, Chester A: Changes in the Weights of the Various Parts, Systems and Organs in Albino Rats Kept at Birthweight for Various Periods, Am. J. Physiol. **48**:67, 1919. Ibid., Weights of Various Parts of the Brain in Normal and Underfed Albino Rats at Different Ages, J. Compar. Neurol. **29**:511, 1918.

27. Variot and Lassablière: Autonomie du développement de l'encéphale dans les retards de la croissance chez les jeunes enfants, Compt. rend. Soc. de biol. **66**:106, 1909.

The present series (Table 2) show an apparent underweight of the spinal cord in such rats when amply refed to a body weight of 25 to 75 gm. The only exception is in the first group (A), which shows a slight excess of 5.4 per cent. The deficits in the other groups are small and probably insignificant, except in Groups E and F. Here the deficits of 7.5 and 11.2 per cent. suggest that the longer underfeeding period may have an inhibitory after effect on the growth of the spinal cord, similar to that found in the brain.

Donaldson[25] likewise observed an increase in the spinal cord of rats held at maintenance by underfeeding from 30 to 51 days of age, and Hatai[8] found a recovery of normal weight in rats subjected to partial starvation at 1 month of age and then placed on full normal diet. Jackson[15] found an increase of 36 per cent. in the weight of the spinal cord of rats held at maintenance from 3 to 10 weeks of age, and Stewart[2] showed that normal relative weight of the cord was obtained within two weeks of ample refeeding.

Eyeballs.—In rats underfed from birth to 3, 6 or 10 weeks, Stewart[3] (1918) found a relative increase in the weight of the eyeballs (compared with normal controls of the same body weight) amounting to 41, 34 and 66 per cent., respectively.

The present data (Table 2) indicate a small overweight (with one exception) in such rats amply refed to from 25 to 75 gm. in body weight. As the excess in but one case (Group D) exceeds 10 per cent., the interpretation is somewhat doubtful. It is possible that the overgrowth of the eyeballs during inanition may persist somewhat longer than in other organs during the subsequent refeeding period.

A continued growth of the eyeballs was observed by Jackson[15] in rats held at maintenance by underfeeding from 3 weeks of age for various periods. At 10 weeks the excess was 50 per cent. In such rats, Stewart[2] found a recovery of normal weight in the eyeballs after 4 weeks of refeeding.

Hypophysis and Pineal Body.—In rats underfed from birth to 3, 6 or 10 weeks of age, Stewart found in the weight of the hypophysis relative increases of 33, 8 and 24 per cent., respectively. No sexual difference in the weight of the organ appeared under these conditions.

The present data (Table 2) indicate that in such rats amply refed to reach a body weight of from 25 to 75 gm., the hypophysis has returned nearly to normal relative weight, the differences being probably within the range of normal variation and experimental error. There is in Group C a sexual difference in the size of the normal hypophysis, as seen in Groups D and E, where the same control rats are separated according to sex. If in Group C the controls and test

rats are grouped separately according to sex, however, the test rats show a decrease in the hypophysis of both sexes, the result being similar to that shown in the table, where the sexes are combined.

In rats held at maintenance by underfeeding from 3 to 10 weeks of age, Jackson[15] noted an increase of 18 or 19 per cent. in the weight of the hypophysis. The normal difference according to sex did not appear. In such rats, on ample refeeding, Stewart[2] found the hypophysis weight somewhat variable, but apparently within the normal range of variation. The volumetric and histologic changes in the hypophysis during inanition and refeeding have been described in detail by Jackson.[28]

The pineal body appears to undergo no constant change in weight in rats underfed from birth to 3, 6 or 10 weeks of age, according to Stewart[3] (1918).

As seen in Table 2, the present data, with one exception (Group D) show in such rats when amply refed to from 25 to 75 gm. body weight a relative loss in the weight of the pineal body, varying from 5.6 to 25.2 per cent. This would seem to indicate that early inanition (especially when prolonged) tends to inhibit the later growth of the pineal body. But the small size of the gland and the relatively few observations makes the conclusion somewhat uncertain.

In rats held at maintenance from 3 to 12 weeks of age, Stewart[2] found an apparent loss in the weight of the pineal body, with recovery after from two to four weeks of refeeding. In rats underfed for longer periods, the results were variable. No sexual difference appears in the weight of the pineal body, as has been found to occur normally in the hypophysis, suprarenal and parathyroid glands (Hatai, Jackson).

Thyroid Gland.—In rats underfed from birth to 3, 6 or 10 weeks of age, Stewart[3] (1918) found no constant change in the relative weight of the thyroid gland.

In the present series (Table 2) there appears to be a slight relative loss (4.0 to 15.6 per cent.) in the rats underfed from birth and refed to 25 or 50 gm. body weight. The three groups refed to 75 gm. are above normal, though in all the differences (4.9 to 7.2 per cent.) are probably within the range of normal variation.

In rats held at maintenance from 3 to 10 weeks of age, Jackson[15] found a marked loss in the weight of the thyroid gland. Stewart[2] concluded that such rats (after maintenance from 3 to 12 weeks of age) on ample refeeding four weeks or more had probably regained normal thyroid weight, although there appeared a slight deficit of

28. Jackson, C. M.: Effects of Inanition and Refeeding on the Growth and Structure of the Hypophysis in the Albino Rat, Am. J. Anat. **21**:321, 1917.

6.2 per cent. The histologic changes in the thyroid and parathyroid glands during inanition are described by Jackson.[29]

Thymus.—During inanition in young rats, the thymus undergoes the well-known "hunger involution" which has been described in detail by Hammar and his pupils. In rats underfed from birth to 3, 6 or 10 weeks, Stewart[3] (1918) found losses in the relative weight of the thymus of 30, 60 and 80 per cent., respectively.

The present data (Table 2) are somewhat variable, indicating that in such rats amply refed to body weight of from 25 to 75 gm. the thymus in most cases still remains somewhat below normal weight.

In rats held at maintenance from 3 to 10 weeks of age, Jackson[15] found a loss of 90 per cent. in the weight of the thymus. According to Stewart,[2] this loss is fully recovered after between two and four weeks of ample refeeding. At four weeks of refeeding there was even an apparent "overcompensatory" growth of the thymus, which does not appear in the present series of experiments.

Jonson[30] underfed a rabbit (6 weeks old) for 31 days, the body weight increasing meanwhile from 553 to 655 gm. After ample refeeding for 3 weeks, the weight of the thymus was found equal to that of a normal control killed at 6 weeks of age. Salkind[31] found that at least one week of refeeding is required to restore the normal lymphoid structure of the thymus in (adult) rats after two days of acute inanition.

Heart.—In rats underfed from birth, Stewart[3] (1918) found little change in the weight of the heart at 3 weeks of age, but a relative increase of 13 per cent. at six weeks and of 27 per cent. at ten weeks.

The present data (Table 2) show the heart practically normal in weight in such rats amply refed to 25, 50 and 75 gm. in body weight after underfeeding from birth to 3 or 6 weeks. The apparent increases (19.3 and 13.8 per cent.) on refeeding after underfeeding from birth to 10 weeks are of doubtful significance.

In rats held at maintenance for various periods beginning at the age of 3 weeks, Jackson[15] found the heart nearly normal in weight. On refeeding after maintenance from 3 to 12 weeks of age, Stewart[2] found the heart probably nearly normal in weight, though somewhat above the Wistar norm in the earlier stages of refeeding.

Lungs.—In rats underfed from birth to the age of 3, 6 or 10 weeks, Stewart[3] (1918) found the weight of the lungs about 26 per cent. below that of normal controls with the same body weight.

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29. Jackson, C. M.: Effects of Inanition on the Structure of the Thyroid and Parathyroid Glands of the Albino Rat, Am. J. Anat. **19**:305, 1916.

30. Jonson, A.: Studien über die Thymusinvolution. Die Akzidentelle Involution bei Hunger, Arch. f. mikr. Anat. **73**:390, 1909.

31. Salkind, J.: Contributions histologiques à la biologie comparée du thymus, Arch. de zool. exper. **55**: Fasc. 5, 1915.

The present data (Table 2) indicate that the lungs in such rats underfed from birth to 3 or 6 weeks and then amply refed to a body weight of from 25 to 75 gm. have usually recovered their normal weight. The apparent overweight in the lungs in those refed after underfeeding to 10 weeks is perhaps due to unrecognized pathologic conditions, which frequently occur in the lungs of the older rats.

In rats held at maintenance by underfeeding from 3 weeks of age for various periods, an average loss of about 15 per cent. in the weight of the lungs was observed by Jackson.[15] Stewart[2] found that in such rats the lungs regained their normal weight within the first weeks of ample refeeding, with an apparent overweight after longer periods of refeeding.

Liver.—In rats underfed from birth to 3, 6 or 10 weeks of age, Stewart[3] (1918) noted increases of 17, 83 and 64 per cent., respectively, in the relative weight of the livers.

The present data (Table 2) are somewhat irregular, but indicate that in such rats amply refed to a body weight of from 25 to 75 gm. the liver weight, as a rule, is probably within the limits of normal variability.

In rats held at maintenance by underfeeding from the age of 3 weeks, Jackson[15] found that the liver tends to gain in weight in the earlier periods, but to lose in weight later. On ample refeeding after maintenance from 3 to 12 weeks of age, Stewart[2] found the liver normal in weight after one week. There was some apparent hypertrophy (probably due to accidental variation) in the rats refed four weeks or more.

Spleen.—In rats underfed from birth to 3 weeks of age, Stewart[3] (1918) found a loss of 49 per cent. in the relative weight of the spleen, while in those underfed from birth to 6 or 10 weeks there was a gain of 31 or 23 per cent., respectively.

The present data (Table 3) indicate that on ample refeeding of such underfed rats there is found an overweight of the spleen at body weight of 25 gm. (52.1 per cent.), and of 50 gm. (33.8 and 112 per cent.); but normal or underweight on refeeding to 75 gm. (—24.3 and —11.4 per cent.). This suggests a tendency to overcompensatory growth on refeeding for a short time, with a tendency to lag behind later.

This idea is supported by results of inanition experiments beginning on somewhat older rats. In rats held at maintenance from 3 weeks of age, Jackson[15] found the spleen nearly normal in weight at 6 weeks, with considerable decrease later (—42 per cent. at 10 weeks). On amply refeeding such rats after maintenance from 3 to 12 weeks

of age, Stewart[2] found rapid recovery of the normal weight of the spleen in one-half week, followed by apparent overgrowth (over-compensatory hypertrophy?) in the following two weeks, but with normal weight after four weeks or more of refeeding. Final conclusions must be guarded, however, since in weight the spleen is known to be one of the most variable organs in the body (Jackson[4]).

Stomach and Intestines.—The stomach and intestines are of especial interest in connection with the subject of inanition. They will be considered first in regard to their weight and second in regard to length.

A. Weight of Stomach and Intestines.—In rats underfed from birth to 3, 6 or 10 weeks, Stewart[3] (1918) found increases of 24, 54 and 98 per cent., respectively, in the relative weight of the empty stomach and intestines (including mesentery and pancreas). In the stomach and intestine with contents, there was a loss of 25 per cent. in weight at three weeks, with gains of 104 and 55 per cent. above normal at 6 and 10 weeks, respectively.

The present data (Table 2) indicate that on refeeding such rats to body weight of from 25 to 75 gm., the empty canal apparently remains above normal weight in all except Group D. Those underfed from birth to 3 weeks have become practically normal at body weight of 75 gm., however. The others may require a longer time to reach the normal proportions. The canal with contents appears in general more nearly normal in weight.

In rats held at maintenance from 3 weeks to 6, 8 or 10 weeks of age, Jackson[15] found the empty stomach and intestines increased in weight 60, 48, and 28 per cent., respectively. Somewhat similar increase was also found in the canal with contents, which are watery or mucous in character in the rats during inanition. On refeeding after maintenance from 3 to 12 weeks of age, Stewart[2] found the tract, both empty and with contents, usually returned to nearly normal weight after two weeks.

B. Length of Intestines.—The growth changes previously described in the weight of the alimentary canal during inanition might be due to changes in length, in caliber or in thickness of the wall. Some measurements on the lengths of the large and small intestine have therefore been made by Stewart, and the average data are recorded in Table 3. The intestines were measured in an extended condition, after being slit open for the entire length, the contents and mesentery being removed. In addition to the rats listed in Table 1, some observations on other individuals, used in other investigations by Stewart[3] (1918 and 1919) are included.

Unfortunately, the length of the stomach was not recorded, so the canal as measured is not strictly comparable with the weight given in Table 2. The approximate weight of the intestines (plus mesentery), however, may be estimated by subtracting the corresponding weight of the stomach and pancreas, according to the data of Hatai.[32] The result indicates that the curve of growth in the weight of the intestines alone is somewhat similar to that for the entire tract. The weight of the intestines apparently increases much more rapidly than the body weight, its relative (percentage) weight increasing about fourfold between birth and the age of 6 weeks. In the meantime, as shown by the data in Table 3, the length of the intestines has also increased more rapidly than the body length, their ratio increasing from about 4.3 at birth to 7.3 at 49 days of age. This relative increase in the length of the intestine is insufficient alone to account for its increase in weight, however, hence there must also be a certain amount of increase in its caliber or in thickness of the wall, or both.

As to relative lengths of the large and small intestine (Table 3, A), in all except the new-born group the ratio remains fairly constant between 7.4 and 7.8. This would indicate somewhat uniform rate of growth in length in both large and small intestines.

In the groups underfed from birth (Table 3, B), there is a marked increase in the lengths of both large and small intestines, which is especially marked in those held at birth weight for 19 days and those underfed to 10 weeks of age. This agrees with the increased weight of the tract, observed by Stewart[3] (1918 and 1919). In the group held at birth weight, the relative increase in length appears greater in the large intestine (+81 per cent.) than in the small (+25 per cent.). In the remaining groups, the increase appears to affect both large and small intestines more nearly in equal proportion.

In the rats amply refed after underfeeding from birth to 3, 6 and 10 weeks of age, the intestines in general still appear relatively long (compared with normal controls of the same body weight) in the rats refed to body weight of 25 gm. In those refed to 50 gm. the intestinal length is usually a little above normal, and in those refed to 75 gm., a little below normal. Excepting the latter group, the changes in length of the intestines in the refed groups correspond in general to the changes in weight of the canal (including stomach) previously shown. There is not much change in the relative lengths of the large and small intestines, as indicated by their ratios (Table 3).

32. Hatai, S.: On the Weight of the Epididymis, Pancreas, Stomach and of the Submaxillary Glands of the Albino Rat (*Mus norvegicus albinus*) According to Body Weight, Am. J. Anat. **24**:71, 1918.

Suprarenal Glands.—In rats underfed from birth to 3 or 6 weeks, Stewart[3] (1918) found a relative increase of about 60 per cent. in the weight of the suprarenals, while in rats underfed to 10 weeks the increase reached 114 per cent.

The present data (Table 2) indicate that in such rats amply refed to 25, 50 and 75 gm. body weight the suprarenals have returned nearly to normal proportions. Groups B and C show essentially the same result when the data are treated separately according to sex, so they are combined in the table for economy of space. Group A is below the weight at which a sexual difference in the weight of the suprarenal appears.

In rats held at maintenance from 3 weeks of age, Jackson[15] found a slight increase in the weight of the suprarenals at 6 and 8 weeks, with a marked increase at 10 weeks (39 per cent. in males, 12 per cent. in females). On refeeding such rats fully after maintenance from 3 to 12 weeks, the suprarenals appeared slightly below the controls in weight during the first four weeks, and normal thereafter. The volumetric and histologic changes in the suprarenal during inanition and refeeding are discussed in detail by Jackson.[33]

Kidneys.—In rats underfed from birth to 3, 6 or 10 weeks of age, Stewart[3] (1918) finds in the kidneys increases in relative weight amounting to 21, 45 and 38 per cent., respectively.

The present data (Table 2) indicate that in such rats amply refed to a body weight of 25 to 75 gm. the kidneys have in general returned to nearly normal proportionate weight. In Groups E and F, the kidneys are still above normal (17.9 and 14.7 per cent., respectively), possibly because sufficient time has not yet elapsed to allow full recovery of the normal proportions.

In rats held at maintenance from 3 weeks of age, Jackson[15] found a definite tendency to increase in weight of the kidneys at 6 and 8 weeks, with but slight increase (+4.1 per cent.) at 10 weeks. On refeeding fully after maintenance from 3 to 12 weeks of age, Stewart[2] found the kidneys normal in weight throughout the various periods.

Testes and Epididymides.—In rats underfed from birth to 3, 6 and 10 weeks of age, Stewart[3] (1918) found the testes 188, 62 and 51 per cent., respectively, above normal weight. The epididymides showed corresponding gains of 95 and 13 per cent. at 3 and 6 weeks, with a loss of 6 per cent. at 10 weeks of age.

The present data (Table 2) indicate that in such rats the relative overweight of the testes at the end of the underfeeding period appar-

33. Jackson, C. M.: The Postnatal Development of the Suprarenal Gland and the Effects of Inanition on Its Growth and Structure in the Albino Rat, Am. J. Anat. **25**: No. 3, 1919.

ently persists to a certain extent (+17.5 and 19.2 per cent.) in the rats amply refed to a body weight of 25 or 50 gm. In those refed to 75 gm., the marked loss (—44.6 and —49.4 per cent.) suggests that possibly the earlier inanition in some way affects unfavorably the later growth of the testes. The effects on the epididymides are not so marked, but they also show subnormal weight in the groups refed to a body weight of 75 gm.

In rats held at maintenance from 3 to 10 weeks of age, Jackson[15] found an increase of 34 per cent. in the weight of the testes, with uncertain results in the epididymides. On refeeding after maintenance from 3 to 12 weeks of age, Stewart[2] obtained somewhat variable results; the testes and epididymides appeared somewhat below normal in the earlier refeeding periods, but normal later.

Ovaries.—In rats underfed from birth to 3, 6 and 10 weeks of age, Stewart[3] (1918) found relative increases in the weight of the ovaries amounting to 83, 91 and 54 per cent., respectively.

The present data (Table 2) for the ovaries in such rats amply refed to a body weight of 25, 50 or 75 gm. are somewhat variable and inconclusive. Those refed after underfeeding to 3 weeks show a moderate overweight (+22.3 and +15.8 per cent.) at 25 and 75 gm., but a slight loss (—3.7 per cent.) at 50 gm. Those refed after underfeeding to 10 weeks show a marked loss (—20.4 and —28.6 per cent.), suggesting that the prolonged inanition period may affect unfavorably the later growth of the ovary.

In rats held at maintenance from 3 weeks of age, Jackson[15] found a slight gain in the ovaries at 6 weeks, but a marked loss (—27 per cent.) at 10 weeks. In rats refed after maintenance from 3 to 12 weeks of age, Stewart[2] found a tendency to overweight of the ovaries in the earlier refeeding periods, normal after four weeks, and underweight in adults. Conclusions are difficult on account of the large variation in the weight of the ovaries due to their normal functional cycles, but the evidence indicates that early inanition may permanently affect the later growth of the ovaries, even though the unfavorable effects may apparently disappear for a time during the earlier periods of refeeding.

DISCUSSION

From previous investigations (cf. summary by Jackson and Stewart[1] (1918), it is known that the growth of the various organs and parts in underfed young rats varies greatly, not only in different organs, but in the same organ according to the age of the animal and the extent and severity of the inanition period. Organs which in early and shorter periods of inanition increase considerably in weight may later barely maintain themselves or may even lose weight. In general, as

age advances, the growth reactions in organ weights during inanition tend to approach those found during inanition in adults. Generally speaking, the growth reaction of an organ in a young animal during inanition will vary according to the intensity of normal growth in that organ at a corresponding normal body weight, but there are numerous exceptions to this rule. The most striking growth reactions in many of the organs are found in rats held at birth weight for two or three weeks, a period when the normal growth rate in general is most rapid (Stewart,[3] 1919).

Since the normal growth rate and the growth during inanition vary so greatly according to age and other factors in the various organs, it would naturally be expected that the rate and extent of recovery on ample refeeding might likewise vary according to circumstances. The evidence at present available demonstrates that this is the case in young rats refed after different periods of inanition. We have seen in the present series of experiments that the results in some organs vary, not only according to the length of the refeeding period (whether to 25, 50 or 75 gm. body weight), but also according to the length of the preceding inanition period.

That the process of recovery on refeeding will also vary according to the age at which the preceding inanition period began is evident if the results of the present experiments (beginning at birth) are compared with those published earlier by Stewart[3] (1918), in which the rats were amply refed after maintenance by underfeeding beginning at 3 weeks of age. In the rats in which the inanition tests began at the later age, most of the organs (excepting the testes, epididymides and suprarenals, which remained subnormal) had recovered approximately their normal relative weight within from two to four weeks of refeeding. The thymus, and possibly the lungs, spleen and ovaries, were apparently even above normal (overcompensatory growth?) after from two to four weeks of refeeding. In the present experiments, in which the underfeeding began at birth, we find somewhat different results. In general, inanition at the earlier age seems to have effected more permanent results, as reflected in the more tardy recovery of normal weight in several of the organs. The suprarenals, it is true, do not appear subnormal; but to the testes and epididymides we must add (for the present series) the cartilaginous and the dry skeleton; brain, spinal cord, thymus, and perhaps the pineal body, thyroid gland and ovaries, as showing more or less retarded recovery in weight on refeeding. There is no evidence of overcompensatory growth in the thymus and ovaries of the present series, and the overweight of the lungs in both cases is perhaps abnormal. In the present series, however, there usually appears a distinct hypertrophy of the

intestinal canal, and possibly of the eyeballs. The possibility of an early overcompensatory growth in the spleen as well as the testes, followed by later retardation in growth, is also recognized.

There is some difficulty in making direct comparison between the present series and that of Stewart,[2] as they differ more or less in the length of the preceding inanition and subsequent refeeding periods, as well as in the age at which the experiments began. Moreover, it must always be remembered that the number of observations is too small for anything but provisional conclusions. More extensive data will doubtless modify the results to some extent. The final effects on the various organs in the rats underfed at different periods and later refed to their maximum size (adult) will be considered in a separate article.

SUMMARY

From the data in the present series of refeeding experiments, the following provisional conclusions are indicated:

1. In albino rats underfed from birth to 3, 6 or 10 weeks of age, rapid growth in body weight ensues on ample refeeding. Body weights of from 25 to 75 gm. are apparently reached more rapidly in those refed after underfeeding to 10 weeks of age than in those refed after underfeeding for shorter periods.

2. The body length remains slightly above normal in the group refed to 25 gm. body weight, but appears nearly normal in the others. The tail length and the weights of the head, limbs and trunk appear nearly normal in all the refed groups.

3. As to the body systems, the integument appears subnormal in weight in the group refed to 25 gm., usually normal (or above) in the others. The ligamentous skeleton appears nearly normal in all refed groups, but the cartilaginous skeleton (moist or dry) tends to be subnormal in weight. The musculature is nearly normal in weight, with a slight apparent deficit in the later refeeding periods. The visceral group (as a whole) and the "remainder" show no constant or significant variations in the refed groups.

4. The individual organs differ greatly in the extent to which they have recovered their normal weight (compared with that in controls of the same body weight) in the various groups refed to a body weight of 25, 50 or 75 gm. after underfeeding from birth to 3, 6 or 10 weeks of age. The weights of the various organs in the refed rats are as follows.

The hypophysis and suprarenal glands are apparently nearly normal in weight in all groups; likewise the heart, lungs and kidneys, excepting an apparent overweight (of doubtful significance) in the groups

refed after underfeeding to 10 weeks of age. The liver is rather irregular in weight, but probably within the range of normal variation.

The brain, spinal cord and thymus appear almost constantly subnormal in weight in all test groups. The apparent loss in the pineal body is of somewhat uncertain significance. The thyroid gland appears subnormal on refeeding to 25 and 50 gm. after underfeeding to three weeks; otherwise normal. The ovaries are irregular in weight, apparently subnormal in those refed after underfeeding to 10 weeks. The epididymides appear subnormal on refeeding to body weight of 75 gm.

The empty stomach and intestines are usually above normal weight in the refed groups; the canal with contents appears more nearly normal in weight. The length of the intestines is somewhat above normal on refeeding to 25 gm. body weight; nearly normal later. There is little change in the relative lengths of large and small intestines. The eyeballs show a slight overweight, of doubtful significance.

Two organs show an apparent tendency to overcompensatory growth in the earlier stages of refeeding, with later retardation. The spleen is greatly above normal weight at body weight of 25 or 50 gm.; but normal or subnormal at body weight of 75 gm. The testes show a similar reaction, the apparent atrophy in the later stages of refeeding being especially marked.

THE MEASUREMENTS OF 250 FULL-TERM, NEW-BORN INFANTS *

ROOD TAYLOR, M.D., Sc.D.

CHILDREN'S CLINIC OF MINNEAPOLIS

In December, 1914, at the suggestion of Dr. J. P. Sedgwick, who offered his material in the University Hospital (Minnesota), the writer began making measurements of new-born infants. This work was pursued until May, 1917, and in all, 250 infants, 125 of each sex, were measured. No attempt was made to measure all the infants admitted to the service, nor was there any attempt at selection, provided they were normal and born at term. Eighty-one per cent. of the babies were measured on the fourth, fifth and sixth day of life, none earlier than the second, and none later than the tenth, the purpose being to allow time for birth traumas to subside and to forestall changes due to extra-uterine growth. The measurements taken were:

1. The total length from vertex to sole.

2. The head and neck height — the distance from the plane of the vertex to that of the shoulder.

3. The distance between the plane of the vertex and that of the navel.

4. The sitting height — the distance between the plane of the vertex and that of the tuber ischii.

5. The arm length — from the acromion to the tip of the second finger.

6. The hand length — from the fold at the base of the hand to the tip of the second finger.

7. The leg length — from the great trochanter to the heel.

8. The foot length — from the heel to the tip of the toes.

9. The intertrochanteric diameter.

10. The hip breadth — the greatest distance between the iliac crests.

11. The shoulder breadth — the distance between the tissues overlying the humeral tuberosities.

12. The chest circumference at the level of the nipples.

13. The occipitofrontal circumference.

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* From the Department of Pediatrics, University of Minnesota. The individual measurements which form the basis of this paper have been placed on file in the Wistar Institute of Anatomy.

14. The distance from finger tip to finger tip with the arms fully spread. The span.

15. The trunk length — the distance from the plane of the vertex to that of the tuber ischii.

16. The head height; that is, the distance between the plane of the vertex and that of the foramen magnum, the latter being determined as advised by Mall by extending a line from the external canthus through the middle of the ear to the occipital region. Because of the different degrees of neck flexion maintained by vigorous infants, this measurement of head height is more or less inaccurate in individual cases. The average figures for head height are probably approximately correct.

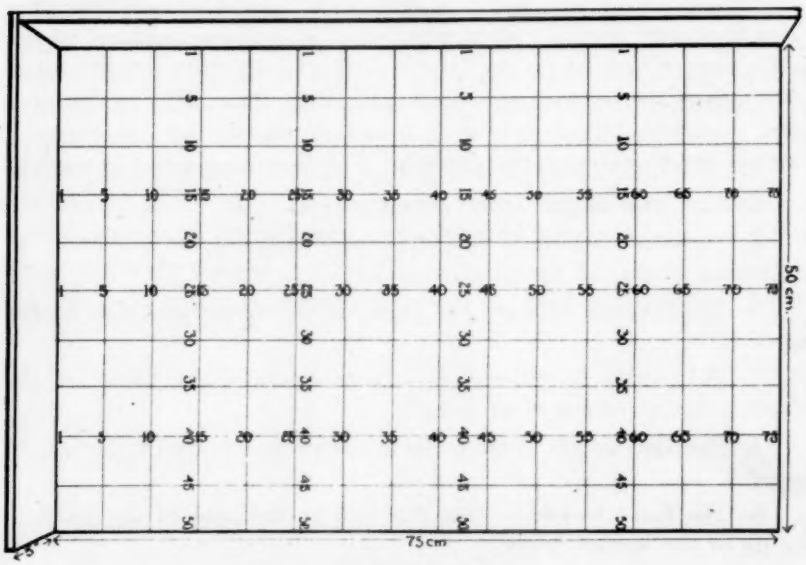

Fig. 1.—Measuring board.

The apparatus used consisted of a rectangular baseboard having sideboards at two edges accurately fitted so as to make an angle of 90 degrees with the baseboard. The baseboard was covered with ruled millimeter paper over which was tacked a sheet of celluloid. Distances in centimeters from the sideboards were marked in ink on the millimeter paper.

The infant was laid on the celluloid sheet with his head held firmly against one sideboard while his left shoulder touched the other. The plane of the foramen magnum was determined, as already mentioned, by passing a straight edge from the external canthus through the middle of the ear to the baseboard, and the distance from the plane of the vertex read directly from the graduations on the baseboard.

A T-square was used to determine the plane of the upper border of the navel, and its distance from that of the vertex read therefrom.

The plane of the shoulder was determined by passing a straight edge vertically down over the acromion to the baseboard. The plane of the tuber ischii was obtained by flexing the thighs to a right angle and laying the straight edge parallel with the buttocks down to the baseboard. The distance from finger tip to finger tip was measured directly with the millimeter tape, the babe lying supine with the arms and hands fully extended at right angles to the trunk. The various diameters were ascertained with a craniometer. The remaining measurements were made directly with a steel millimeter tape.

Somewhat similar measurements have been made of German babies by Weissenberg,[1] and of French infants by La Faille.[2] Because it is possible that racial characteristics affect the relative size of different portions of the body, and since the mingling of races in this part of the United States has only begun, the writer, in each instance, tabulated the ancestry of the baby's mothers. Where she was descended from an already mixed stock, her nationality was recorded as American. Table 1 shows the different nationalities represented and the number of each:

TABLE 1.—NATIOALITY OF INFANTS

Nationality	Number	Nationality	Number
Swedish	59	Austrian	6
American	50	French	5
Norwegian	36	Danish	3
German	29	Polish	2
Jewish	28	Negro	2
Finnish	12	Scotch	1
Irish	9	Roumanian	1
English	7		

TABLE 2.—CHEST CIRCUMFERENCES

Day Measured	Males	No. in Whom Chest Cir. Exceeded Aver.	No. in Whom Chest Cir. Was Less Than Aver.	Females	No. in Whom Chest Cir. Exceeded Aver.	No. in Whom Chest Cir. Was Less Than Aver.
2	..	..	..	1	..	1
3	8	5	3	6	2	4
4	57	30	27	57	23	34
5	25	12	13	32	9	23
6	16	12	4	16	10	6
7	9	5	4	7	3	4
8	5	3	2	1	1	0
9	3	1	2	3	1	2
10	..	..	..	2	2	0

Linzemeyer[3] has reported that a marked change in the horizontal chest circumference takes place shortly after birth. My data on this subject are shown in Table 2.

1. Weissenberg, S.: Die Körperproportionen des Neugeborenen, Jahrb. f. Kinderh., **64**:839, 1906.
2. La Faille, L.: Quelques mensurations du foetus, Thèse de Paris, 1893.
3. Linzenmeier, G.: Ztschr. f. Geburtsh. u. gynäk. **76**:242, 1915.

In Table 3 the vertical arrangement of the general averages shows the proportional values. One notices the constant preponderance of males over females; that from finger tip to finger tip is further than from crown to heel; that the occipitofrontal circumference is barely greater than the sitting height, but decidedly outmeasures the chest circumference; that the trunk length is greater than the arm, and the latter longer than the leg. At the extreme right are placed such of Weissenberg's figures as are comparable. One notes that in the German babies the vertex to sole measurement is greater than that of the outstretched arms — a finding at variance both with my figures and those of La Faille. Further, the proportionate occipitofrontal circumference of the new-born German infant is less than that in the American babes. Weissenberg's somewhat greater figures for arm and leg length are probably more accurate than those of the writer. The former worked in the dead house, while the latter found it almost impossible to completely extend the extremities of the living infant. Weissenberg measured about sixty babes, La Faille 105. They found the same proportion between trunk length, arm length and leg length as the writer (Table 3).

TABLE 3.—Proportion Between Trunk, Arm and Leg Lengths

	Males, Weights in Gm.			Females, Lengths in Mm.			Weissenberg's Average		
	Maximum	Minimum	Average	Maximum	Minimum	Aver. age	General Average	Male	Female
Weights	4,890	2,515	3,484	4,325	2,450	3,377	3,430		
Finger tip to finger tip, arms outspread	573	450	515	588	460	505	510	486	480
Total length	570	452	512	568	450	500	506	508	500
Occopitofrontal circumference	378	298	347	368	306	341	344	327	326
Sitting height	377	312	343	374	292	339	341	333	333
Chest circumference	358	280	323	415	284	321	322	282	285
Trunk length	260	190	224	258	189	224	224	214	212
Arm length	234	176	203	222	180	197	200	214	210
Leg length	220	162	190	221	158	188	189	205	203
Shoulder breadth	142	104	121	137	104	119	120		
Head and neck height	134	105	119	130	100	115	117		
Interochanteric diameter	101	77	91	101	78	89	90		
Head height	99	72	84	95	70	83	84		
Foot length	96	67	83	92	72	81	82	78	78
Hand length	84	62	72	78	60	70	71	64	64

As regards individual variation, the spread of arms was as long as or longer than the body length in 81 boys and 82 girls, 65 per cent of the total. The head circumference was greater than that of the chest in 119 boys and 120 girls; the trunk length was greater than the arm length in 119 boys and 123 girls, and greater than the leg length in 123 boys and 124 girls. The arm length exceeded the leg length in 111 boys and 107 girls. In the boys the midpoint of the body lay

at or above the navel in 114 and below it in 11, the extreme figures being 32 mm. above and 10 mm. below. It was at or above the navel in 100 girls and below in 25; the female infants showed greater variations, the extremes being 36 mm. above and 14 mm. below.

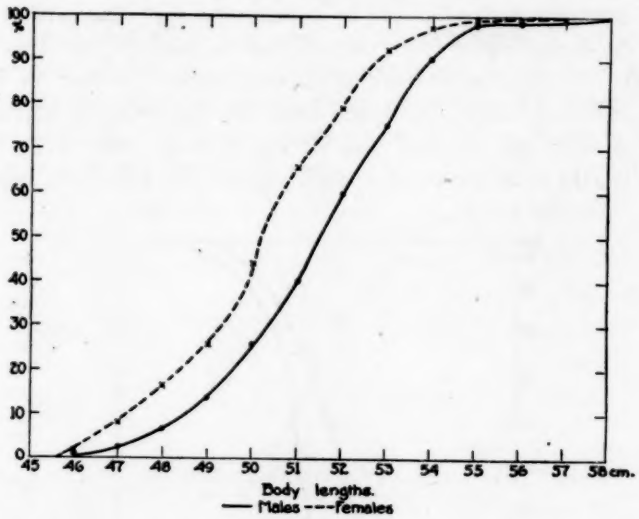

Fig. 2

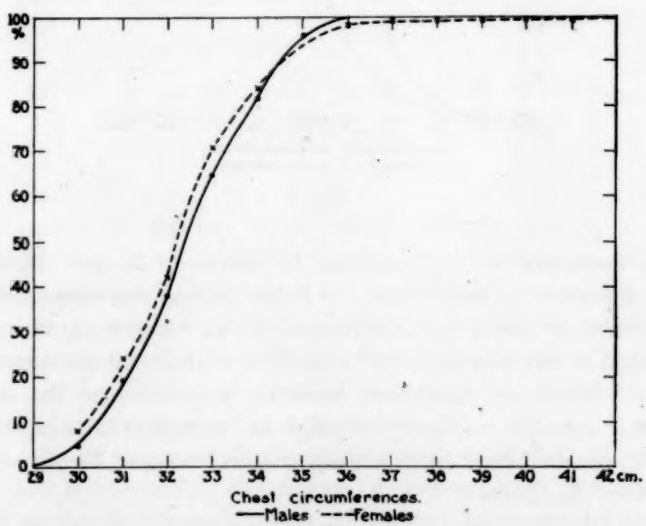

Fig. 3

Kakuschkin[4] has previously noted the greater tendency for the center of the body to lie below the navel in new-born girls. As he

4. Kakuschkin, N.: Zur Topographic des Nabels bei Frauen und Neugeborenen, Monatschr. f. Geburtsh. u. Gynäk. **36**:278, 1912.

expresses it: "In new-born girls the supra-umbilical length relative to length of body is less than in boys."

Holt's[5] figures, based on the measurement of 100 full term infants, would indicate that the body center lies 20 mm. below the navel.

The term dispersion is used to indicate the fact that, within a given group, the items differ from one another in size, or, in other words, that there is a lack of uniformity in magnitudes. When we say that the dispersion is slight, we mean that this difference is trivial when compared with the absolute size of the average item while the dispersion is said to be great when such variation is relatively large.

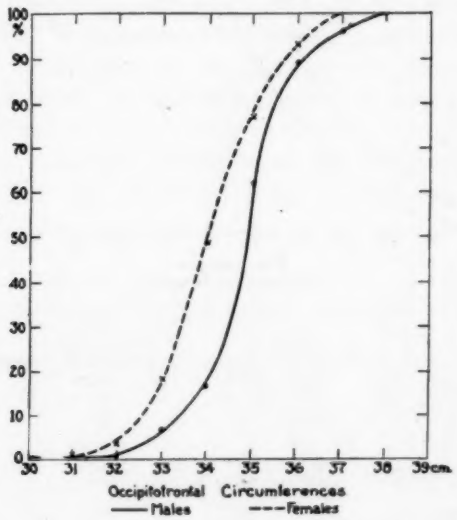

Fig. 4

The dispersion of a group may be measured by the difference in size of the most extreme items; in other words, the *range,* or it may be measured by the general deviation of the items from the average. The range is too indefinite to be used as a practical measure of dispersion. We must, therefore, measure dispersion by the deviation from the average. Dispersion may be measured absolutely. The absolute measure used in this study is the Standard Deviation which is obtained as follows:

If m_1, m_2, m_3 . . . m_n are the items, n in number having respective deviations from the average of d_1, d_2, d_3 . . . d_n, if

5. Holt, L. E.: The Diseases of Infancy and Childhood, New York, Appleton, Ed. 6, 1914, p. 21.

the average magnitude is represented by a–, then the Standard Deviation σ is obtained from the formula:

$$\sigma = \sqrt{\frac{\Sigma d^2}{N}} = \sqrt{\frac{\Sigma (m - a)^2}{N}}$$

It is found that 68.27 per cent. of all the items — for example, 68.27 per cent. of 125 full-term male new-borns — will have a deviation from the average body length of no more than the number corresponding to σ, the standard deviation, the absolute measure of dispersion which in this case is 21 mm.

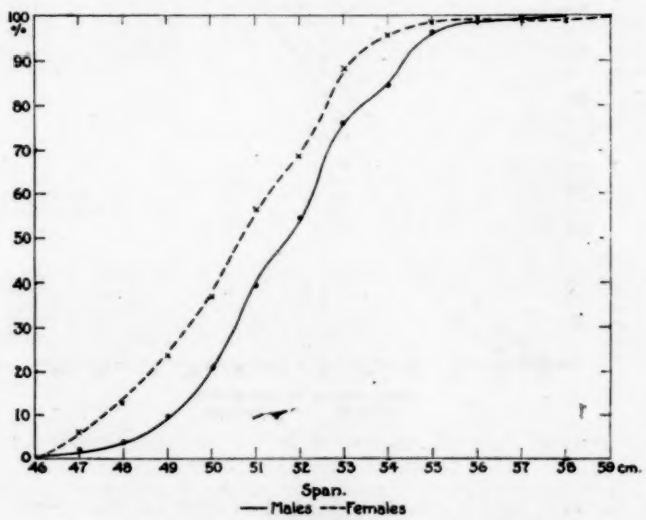

Fig. 5

For comparing statistics from various sources one uses a relative measure of dispersion. This relative measure is known as the coefficient of deviation and is obtained by dividing the standard deviation by the quantity representing the average. In the case of the full-term, male new-born the average body length was found to be 512 mm. and this into the absolute measure of dispersion, the Standard Deviation 21 mm. gives a quotient of 4.1 per cent.

This relative measure of dispersion — the coefficient of deviation is also used in comparing the degree of dispersion in two characteristics of different average magnitude whether measured by the same units or not — as for example the body length, on the one hand, and the spread of arms on the body weight on the other.

If in a large number of instances two variables tend always to fluctuate in the same or opposite directions, a relationship exists which

is called correlation. The measure of the degree of correlation used in this study is that devised by Karl Pearson[6] and called by him the coefficient of correlation.

Where x_1, x_2, x_3, etc., represent one series of deviations from the average of the subject, and y_1, y_2, y_3, etc., represent the series of deviations from the average of the relative—where σ_1 is the standard deviation of the one, and σ_2 the standard deviation of the other — where N equals the total number of pairs of items and r represents the coefficient of correlation then the latter is obtained from the formula

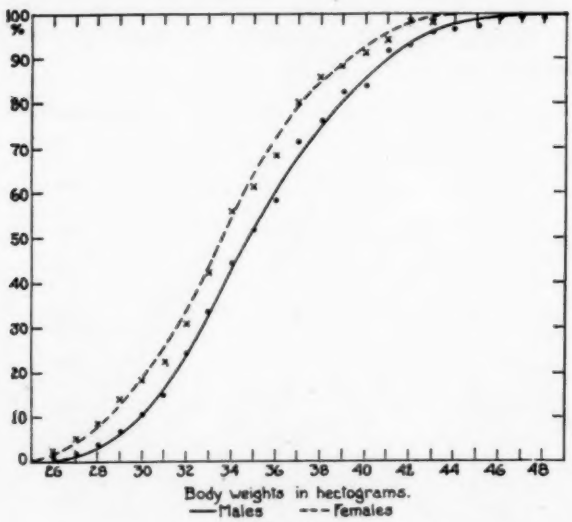

Fig. 6

$$r = \frac{(x\ y)}{n\ \sigma_1\ \sigma_2}$$

A coefficient of +1 indicates perfect direct correlation, one of —1 perfect inverse correlation and one of /.0 no correlation whatever. For example, only direct correlation was observed in this study of the measurements of the new-born and the most perfect correlation found is that between the body length and the spread of arms.

Table 4 contains the mathematical constants of dispersion and correlation derived from the five major measurements. Most of these have never before been determined for the new-born infant.

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6. Pearson: On the Magnitude of Certain Coefficients of Correlation in Man, Proc. Roy. Soc. Lond. **66**:23, 1899.

Table 5 is taken from Pearson's figures for British Infants and is inserted for comparison.

TABLE 4.—Deviations from Standard as Found by Robertson and Pearson

	Average	Maximum	Minimum	Standard Deviation	Coefficient of Deviation, per Cent.
Males:					
Length	512	570	452	21.045 Mm.	4.11
Span	515	573	450	20.898 Mm.	4.05
O. F. circumference	347	378	298	11.27 Mm.	3.24
Chest circumference	323	358	280	15.235 Mm.	4.71
Weight	3,484	4,890	2,515	432.47 Gm.	12.41

	Per Cent.
Coefficient of correlation of weight and length	78.5
Coefficient of correlation of weight and O. F. C.	72.66
Coefficient of correlation of length and O. F. C.	77.39
Coefficient of correlation of O. F. C. and chest	69.7
Coefficient of correlation of length and span	85.737

	Average	Maximum	Minimum	Standard Deviation	Coefficient of Deviation, per Cent.
Females:					
Length	500	566	450	20.4702 Mm.	4.094
Span	505	588	460	22.1273 Mm.	4.38
O. F. circumference	341	368	306	12.2732 Mm.	3.599
Chest circumference	321	415	284	17.7195 Mm.	5.52
Weight	3,377	4,325	2,450	408.55 Gm.	12.09

	Per Cent.
Coefficient of correlation of weight and length	81.34
Coefficient of correlation of weight and O. F. C.	78.2
Coefficient of correlation of length and O. F. C.	79.12
Coefficient of correlation of O. F. C. and chest	68.36
Coefficient of correlation of length and span	86.84

TABLE 5.—Weight and Length of New-Born British Infants, 1,000 of Each Sex (from Pearson)

	Mean		Standard Deviation		Coefficient of Deviation		Coefficient of Correlation, Weight with Length, per Cent.
	Weight, Lbs.	Length, Ins.	Weight, Lbs.	Length, Ins.	Weight, per Cent.	Length, per Cent.	
Females	7.073	20.124	1.006	1.177	14.228	5.849	62.2
Males	7.301	20.503	1.144	1.332	15.664	6.500	64.4

Brailsford Robertson[7] found the standard deviation for the weight of new-born Australian males to be 18.2 ounces, with a coefficient of 14.3 per cent., and for females to be 17.6 ounces, with a coefficient of 14.5 per cent. Pearson and Robertson determined their constants from measurements made routinely in certain hospitals. The lesser degree of correlation and the greater variation which they report are probably explained, first, by the way in which they obtained their data, and secondly, by the fact which is apparent from Pearson's figures, that their material contained many premature babes.

7. Robertson: The Pre- and Post-Natal Growth of Infants, Am. J. Physiol. **37**:1, 1915.

A conception of the degree of variation in my measurements can be obtained from the accompanying graphs. These show cumulative percentage ogival curves, percentages being shown on the ordinates and the corresponding measurements on the abscissae.

From these curves one can obtain the percentage, showing any given measurement or falling in any range concerning which information is desired. For example, on the curve representing occipitofrontal circumference, one finds that 61.6 per cent. of the males had an occipitofrontal circumference of 35 cm. or less; that 16.8 per cent. had an occipitofrontal circumference of 34 cm. or less, and that 44.8 per cent. had an occipitofrontal circumference of between 34 and 35 cm.

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The writer wishes to acknowledge his indebtedness to Prof. F. E. Scammon of the Department of Anatomy of the University of Minnesota for advice as to the choice and graphic treatment of the measurements taken.

Additional references:

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King: Elements of Statistical Method, New York, Macmillan Co., 1915, pp. 14 to 152 and 197 to 215.

PROGRESS IN PEDIATRICS

REVIEW OF RECENT LITERATURE ON THE NEW-BORN

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CHILDREN'S CLINIC OF MINNEAPOLIS

INTRODUCTION

During the last few years the supervision of the new-born child in a number of our best clinics has passed from the hands of the obstetrician into those of the pediatrist, while in private practice the pediatrist is being called on more and more to attend the new-born, one authority stating that after its first breath the little patient belongs to the children's specialist. It is therefore of vast importance that we perfect as best we may our knowledge of the proper means to promote the health and growth of the normal child, and that we be able to recognize at once any unusual condition that may be present, and to institute such treatment as will give these less fortunate children every advantage possible toward proper development.

In order to acquire a comprehensive idea of what has been published during the five years from 1914 to 1918, inclusive, the writer will present a series of papers reviewing the literature, outlining the progress that has been made, and assembling in somewhat concrete form the opinions of our various men on the etiology, pathology and treatment of the diseases of the new-born. Only those diseases or conditions which are recognizable during the first three months of life will be considered, and only that part of any article dealing with the subject of the new-born will be reviewed. The bibliography attached will represent articles which might be of interest to anyone wishing to review the subject more completely.

ANATOMY AND PHYSIOLOGY OF THE NEW-BORN

Blood Analysis.—In examining the literature of the last few years one finds few reports of chemical analysis of the blood in the first days of life. Considerable valuable data have been published on the content of the fetal blood as taken from the cord at birth, it being comparatively easy to obtain in sufficient quantities for chemical analysis. At best, however, this represents more nearly the conditions existing during fetal life than those one might expect to find during the first days after birth. The great difficulty in repeatedly obtaining

blood from the same new-born has greatly curtailed adequate investigation. Since it is possible through the routine puncture of the longitudinal sinus to obtain sufficient quantities of blood for this purpose, and since with the new methods we use very small amounts of blood for the determinations, we may expect more and better work in the future.

Schlutz and Pettibone[1] have determined the nonprotein nitrogen content of the blood in twenty-six newly born infants, and publish a table showing the result of their determinations. The total nonprotein nitrogen of the systemic blood is found to be approximately the same as in the adult, the age and weight of the infant and the period after feeding having no bearing. The percentage of urea nitrogen is uniformly high and averages 50 per cent. of the total nitrogen, and is lowest in the new-born which has not been fed. The amount of ammonia nitrogen is extremely small in every instance and also is not influenced by age or time after feeding. Amino-acids are constantly present even immediately after birth when no feeding has been given.

Slemons and Morriss[2] in an examination of thirty-five normal obstetric patients found that at the time of birth the average rest-nitrogen in the fetal blood was 24.9 mg. per 100 c.c., while the average of urea nitrogen in fetal blood of sixteen normal patients at birth was 10.4 mg. per 100 c.c. The same concentration of urea in the maternal and fetal circulations would indicate that this substance passes through the placenta by diffusion. Asphyxia dependent on impairment of the fetal heart action is attended with a notable increase in the urea of the fetal blood.

In considering the blood fat of the new-born, Marriott and Sisson[3] in a very complete article find that the blood fat is independent of the state of nutrition of the infant. Subcutaneous fat does not necessarily bear any relation to circulating fat. However, the infant who is gaining in weight will have a higher average blood fat than one who is not gaining, and breast fed infants who are gaining in weight have relatively high blood fat percentages.

Huffmann[4] examined the blood from the umbilical cord and reports an almost constant value for cholesterin of from 0.11 to 0.12 per cent.

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1. Schlutz, F. W., and Pettibone, C. J. V.: Quantitative Determination of Nonprotein Nitrogen in Blood of New-Born, Am. J. Dis. Child. **10**:206 (Sept.) 1915.

2. Slemons, J. M., and Morriss, W. H.: Nonprotein Nitrogen and Urea in Maternal and Fetal Blood at Time of Birth, Bull. Johns Hopkins Hosp. **27**:343, 1916.

3. Marriott, W. McK., and Sisson, W. R.: Variations in the Lipoid (Fat) Content of the Blood of Infants Under Certain Nutritional Conditions, Am. J. Dis. Child. **16**:75 (Aug.) 1918.

4. Huffmann: The Cholesterin Content of the Blood, Zentralbl. f. Gynäk. **39**:33 (Jan. 16) 1915.

Slemons and Curtis[5] examining the maternal and fetal blood, find that the total amount of fat and fat-like bodies vary between 600 mg. and 1,200 mg. per 100 c.c. of the maternal blood. The fetal determinations are within much narrower limits, generally from 500 mg. to 700 mg., with most of the results approaching the lower figure. In the fetal blood the total cholesterol-esters were found in the fetal blood, the cholesterol being exclusively in the free form. The difference between the total cholesterol of maternal and fetal blood in cases in which delivery was effected without anesthetic is accounted for by the quantity of cholesterol-esters in the maternal blood. The quantity of free cholesterol is the same in both circulations. The placenta partition is permeable for free cholesterol and impermeable to cholesterol-esters. The blood cholesterol estimations are of value in the clinical examinations of cases of autointoxication.

Sella[6] states that the fats of the fetal liver are mixed lipoids, phosphates, cholesterin and neutral fats. In late pregnancy they are principally ethers of cholesterin. They disappear after birth, the liver being free from fat within a few days.

On testing blood for the uric acid content during the first few days of life, Sedgwick and Kingsbury[7] found in thirty-nine cases, 3 mg. at birth, increasing to 3.9 mg. the third day, falling gradually to 1.6 mg. about the tenth day. They believe there is a parallelism between the high uric acid content of the blood of the new-born and the high excretion of this substance during the first three or four days of life. The human fetal tissue probably possesses no uricolytic power.

Plass[8] refers to Slemons and Morriss' work with whole blood in which they found the concentrations in maternal and fetal bloods collected at time of delivery to be the same. Losse and Van Slyke show that there is no significant variation in the alkali reserve of maternal and fetal blood. The author in nine cases of fetal plasma examination found the average of preformed creatinin to be 1.07 mg. and the total creatinin averaged 1.93 mg. The plasma of the mother and child contained the same amounts, these values being the same as found in nonpregnant women.

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5. Slemons, J. M., and Curtis, Charles S.: Cholesterol in the Blood of Mother and Fetus, Am. J. Obst. **75**:569, 1917.

6. Sella: Lipoids of the Liver in Mother and Fetus, Ann. di ostet. et gin. **1**:111 (March) 1914.

7. Sedgwick, J. P., and Kingsbury, F. B.: Uric Acid Content of the Blood in the New-Born, Am. J. Dis. Child. **14**:98 (Aug.) 1917.

8. Plass, E. D.: Placental Transmission of Creatinin and Creatin in the Whole Blood and Plasma of Mother and Fetus, Bull. Johns Hopkins Hosp. **28**:137 (April) 1917.

Morse[9] in an examination of eighteen normal infants found that the blood at birth contained from 10 mg. to 15.8 mg. of amino-acid nitrogen. The values for whole blood were greater than for plasma, the plasma values being from 9.1 mg. to 11.6 mg. The passage of amino-acid from mother to fetus requires the assumption of absorption properties on part of the placenta. In an additional article under the same title the author gives a differential creatinin content between the whole blood, plasma and corpuscles of the fetal circulation. The whole blood ranged from 3.56 mg. to 6.25 mg. The plasma from 1.15 mg. to 2 mg. The corpuscles from 6.32 mg. to 14.92 mg.

Bang[10] in his research on bile pigment in the blood found that the blood of the umbilical cord always contained a notable amount of bile pigment. He therefore concluded that icterus in the new-born may be considered a physiologic condition. The amount of pigment shows a constant increase in the blood during the first few days, so it is only a question of degree between the new-born with or without clinical icterus.

Lichtenstein[11] in his very complete work on the premature infant reports a considerable degree of anemia in a large percentage of his cases. He recommends from 0.25 gm. to 0.5 gm. of ferrous lactate from one to three times a day. His article covers 297 pages, giving a complete history of the literature with details as to care and feeding of ninety-two infants.

McClanahan and Johnson's[12] article contains a splendid review of the reports on blood examinations of infants since 1910. They report differential leukocyte counts on a large number of children ranging from 3 weeks to 1 year in age; the results of those under 1 month are as follows:

Age	Small Lymph.	Large Lymph.	Polys.	Trans. Eosin.	Eosin.
3 weeks.....	16	26	48	8	2
	21	42	28	9	..
	64	14	16	2	4
1 month.....	19	31	43	7	..
	27	43	26	4	..
	12	32	46	7	3
	25	41	30	4	..
	59	7	29	3	2

9. Morse, A.: Amino-Acid Nitrogen of Blood in Normal and Complicated Pregnancy and in New-Born Infant, Bull. Johns Hopkins Hosp. **28**:199 (June) 1917.

10. Bang, F.: Jaundice of the Newly Born, Hospitalstidende **8**:637 (June 30) 1915.

11. Lichtenstein, A.: Blood Findings in the Prematurely Born, Svenska Läk. Sällsk. Handl. **43**:1533 (Dec. 31) 1917.

12. McClanahan, H. M., and Johnson, A. A.: Brief Report of 68 Blood Examinations of Infancy with a Review of the Recent Literature of the Blood of Infants, Arch. Pediat. **33**:756 (Oct.) 1916.

Very little has been published on the coagulation time of the new-born child during the first few days of life. Shaw and Williams[13] have described several methods for obtaining the coagulation time of human blood. They point out that there are wide variations in results due to different methods and technic. Also there is a wide variation when different operators use the same method and technic, due to personal equation. The variation with different methods on the same blood may be from 2.5 to 34 minutes. The theories of coagulation as set forth by Morawitz, Howell and Berdet and Delange are briefly discussed, and the method for obtaining the coagulation time used by Dale and Laidlaw is described in detail. They tested the coagulation time of 108 healthy infants under 2 years of age by this method, the time ranging from 1 minute and 15 seconds to 1 minute and 48 seconds, the average being 1 minute and 30 seconds. In testing the same children with Brodie's coagulometer the results were, in children under 1 year, an average of 3 minutes and 47 seconds, the longest time being 4 minutes and 42 seconds.

Flusser[14] states that Wright's method of testing the coagulating time is inaccurate. He describes a capillary tube method and reports that the coagulation time by this method in the first two weeks of life is 8¼ minutes in a temperature of from 19 to 29 C. The coagulation time is not effected by dyspeptic erythema, eczema, pemphigus neonatorum, rachitis or cephalhematoma. In icterus neonatorum the time is 11 minutes and 40 seconds or even longer. In nine cases of hereditary syphilis, two had increased coagulation time. In latent hereditary syphilis this characteristic may be found before the earliest symptoms. It passes away after antisyphilitic treatment.

Urine.—The examination of the new-born urine has received a great deal of attention in the past, and the various constituents have been well established for some time. There is very little new work reported in the recent literature.

Schloss[15] has described a simple apparatus for the collection of urine from male infants. It consists of a tube with a constriction and bulb at the lower end which forms a reservoir. This has been in use for some time at Bellevue Hospital and has been satisfactory.

Sedgwick[16] examined the urine of a series of new-borns and some older children for oxalic acid content. Part of the results pub-

13. Shaw, H. L. K., and Williams, F. J.: Bood Coagulation in Infancy, Albany M. Ann. **36**:571 (Dec.) 1915.

14. Flusser, Emil: Coagulability of the Blood in the First Weeks of Life, Monatschr. f. Kinderh. **12**:12, 1914.

15. Schloss, Oscar: A Simple Apparatus for the Collection of Urine from Male Infants, J. A. M. A. **70**:223 (Jan. 26) 1918.

16. Sedgwick, J. P.: Oxalic Acid Excretion in the Urine of Children, Am. J. Dis. Child. **10**:414 (Dec.) 1915.

lished were obtained by the Salkowski and part by the Albahary method, the latter giving consistently higher results. All of the new-born urines examined were collected from normal breast-fed infants. By Albahary's method there was an average daily excretion of oxalic acid amounting to 4.78 mg., the highest individual instance being 9.43 mg. He concludes that inasmuch as the infants were breast fed exclusively, the oxalic acid excreted was of endogenous origin. The oxalic excretion in new-borns is relatively higher than in adults.

Moore[17] examined the urine of new-borns for phenol during the first three days of life. The average daily amount excreted in his nineteen cases was 41 c.c.; average total nitrogen 376 mg. He concludes that phenol is quantitatively present in the urine of all new-borns and is partly, at least, of endogenous origin.

Flamini,[18] examining the urine of new-born children, found the acidity in breast fed infants much less than that of those artificially fed. The urine from the breast fed ranged in acidity from 0.1 to 0.6, while in the artificially fed it ranged from 1.25 to 4.0, and in some cases with bowel trouble it ranged from 4.5 to 5.8. The phosphate content was also higher in the bottle fed. Calcium lactate given to bottle fed infants markedly reduced the acidity of the urine, 1.5 gm. being given at each feeding.

Gittings and Mitchell[19] report that the new-born infant eliminates about the same percentage of phenolsulphonephthalein as the adult. In sixteen cases reported the average for the first hour was 47.7 per cent., and at the end of a two-hour period a total elimination of 69.4 per cent. was found. The patients ranged in age from 3 weeks to 3 months. They recommend the injection of 6 mg. of phenolsulphonephthalein in the lumbar region, collecting the specimen by catheterization at the end of two hours.

Mammary Gland.—There are still a few articles appearing in the literature regarding the mammary secretion of the new-born. Arteaga[20] discusses the question at great length. He believes that the phenomenon is purely a physiologic process and should be present in all new-borns. He does not believe that there is any relation between mammary secretion and falling off of the cord. In fifty-two infants investigated he found that fluid could be expressed from the gland

17. Moore, C. U.: The Phenol Excretion in the Urine of Infants, Including the New-Borns, Am. J. Dis. Child. **13**:15 (Jan.) 1917.

18. Flamini, M.: The Urine Reaction in Infants, Rivista di clin. pediat., Florence **15**:462 (Sept.) 1917.

19. Gittings, J. C., and Mitchell, A. J.: Phenolsulphonephthalein Elimination in Infants and Young Children, Am. J. Dis. Child. **14**:174, 1917.

20. Arteaga, J. F.: Mammary Secretion of the New-Born, Rev. de Med. y Cyrug., Habana, **23**:321, 1918.

from just after birth up until the twelfth or nineteenth day. In 97 per cent. of cases investigated the findings indicated that the fluid was of the nature of a physiologic secretion, independent of sex or breast feeding. The average duration was forty-three days. The obstetric and pathologic antecedents of the mother seemed to have no bearing.

Apert[21] observes that the secretion begins on the third or fourth day. It attains its maximum and commences to decrease on the ninth day, but may persist until the twentieth day. In certain cases the tumefaction and secretion of milk are more marked at a later period, the breasts becoming hard, red and painful. As much as 10 c.c. of milk have been expressed in a few minutes. Local infections at times occur, probably due to attempts at expression of the milk. The writer's analysis of such milk showed that the fat, casein and sugar content is about the same as in mother's milk, but the salts were found in greater quantity — P_2O_5 — 0.844; PO_4Na_2H — 1.688; Cl — 0.994; NaCl — 1.638. The microscopic examination showed nothing different from mother's milk. Vaginal bleeding has been noted in connection with tumefaction of the breast and has been considered a prelude to precocious puberty in females. In males enlargement of the breasts has been noted to occur in conjunction with hypertrophy of the genital glands. In certain new-born infants the same anatomic and physiologic modifications manifest themselves as at time of puberty.

Genital Bleeding.—Zacharias[22] examined 400 new-born girls and reported genital hemorrhage present in ten. There were no symptoms and the hemorrhage subsided in a day or two. From his review of the literature he believes that mild bleeding may be present from four to eight days. All of the ten children in his series were unusually large and well developed, and he considers this to be one of the factors on which the condition depends. He quotes Halban as attributing the bleeding to a hyperemia of the uterus caused by a hormone developed in the placenta. The hemorrhage usually occurs on the sixth or seventh day, and it may be slight or quite marked and is often accompanied by an additional output of mucus.

Initial Loss of Weight.—There is still some difference of opinion as to the exact cause of the initial loss of weight in the new-born. Benestad[23] believes that it is due to an insufficiency of the metabolism, especially of the hydrogen-containing materials. Infection may play an important rôle. Artificial feeding prolongs and increases the loss

21. Apert, E.: Tumefaction of the Breasts and Secretion of Milk in New-Born Infants, Le Nourrisson **2**:239 (Sept.) 1914.

22. Zacharias, E.: Genital Hemorrhage in Newly Born Girl Babies, Ten Cases, Med. Klin. **10**:1643 (Nov. 1) 1914.

23. Benestad, G.: The Cause of Physiological Loss of Weight in the New-Born, Jahrb. f. Kinderh. **80**:21 (July) 1914.

of weight, as it is more difficult for the infant to become accustomed to this ration than to breast milk.

Borrino[24] in his study of 1,110 new-borns finds that the initial loss of weight varies from 100 to 300 gm., reaching a maximum between the second and third days. It does not depend on nursing, but is due to noncompensation for water loss through skin and lungs. The birth weight should be regained from about the eighth day to the end of the second week. Protracted loss or stationary weight would indicate the necessity of medical attention.

Ramsey and Alley[25] in their analysis of clinical charts of 300 new-born infants give the average birth weight for boys as 3,391 gm. and for girls 3,276 gm. The initial loss of weight was about 240 gm., the average time the loss continued being three days. Only one-fourth of the infants regained the birth rate by the tenth day. The average daily gain was about 20 gm. All children were nursed at four-hour intervals.

Schick[26] reports his experiment in attempting to prevent the initial loss of weight in twelve new-borns. He gave each infant 10 per cent. of its body weight of breast milk during the first twenty-four hours, increasing the amount until 15 per cent. was given at the end of the third twenty-four hours. He used the breast milk of mothers having babies less than a week old. He was able to prevent the initial loss of weight in all cases.

Yerington[27] gives the average birth weights estimated from 2,966 weights taken, as 3,500 gm. for males and 3,311.7 gm. for females, the average being 3,432 gm. He states that the initial loss of weight is greater in San Francisco babies by about 38 gm. than the average as given by Holt, but the return to original weight occurs at approximately the same time in infants; that is, ten days. At the end of the first month, Yerington's babies were heavier than those recorded by Newman and Holt. At the end of the first year they are heavier than previously reported from any other locality.

Bailey and Murlin[28] in experiments on the loss of weight in the new-born found that the amount of water loss was 28.12 gm. per

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24. Borrino, Angelas: Physiologic Loss of Weight in New-Born Infants. Pediatria **25**:413 (July) 1917.

25. Ramsey, W. R., and Alley, A. A.: Observations on the Nutrition and Growth of New-Born Infants; an Analysis of 300 Clinical Charts, Am. J. Dis. Child. **15**:408 (June) 1918.

26. Schick, B.: Zur Frage der Physiologischer Korpergewichtsabnahme des Neugebornen, Ztschr. f. Kinderh. **13**:257, 1916.

27. Yerington, H. H.: Clinical Supervision of the Well Baby During the First Year., J. A. M. A. **71**:1043 (Sept. 28) 1918.

28. Bailey, H. C., and Murlin, J. R.: Energy Requirements of the New-Born, Am. J. Obst. **71**:526, 1915.

kilogram for the first 12 hours, 40.74 gm. during the next 24 hours and 53.6 gm. for the second twenty-four hours. They quote Lust as finding a greater amount of dry substance in the blood during the first week than subsequently, and believe that in the new-born there is a close relationship between the body weight and the concentration of the blood. A part of the water loss is permanent and cannot be made up by administration of water. Reason for this will be readily understood when we remember that the child has passed from a water medium to an atmospheric medium. Immediately after birth the skin is turgid with water absorbed from the amniotic fluid and it is twenty-four hours later before it assumes a normal appearance. In August, 1912, because of the decided loss of weight in a large number of new-borns, fifty infants at Bellevue were allowed to nurse for ten minutes and then given a milk mixture similar to colostrum. Only one case developed any adverse symptoms, and that not serious. The initial loss of weight was lessened by this procedure from 50 to 150 gm. The four hour interval was discontinued in favor of the three hour, because of the great loss in weight.

Metabolism.—Chapin[29] has tried out the various formulas for the determination of surface area of infants both by actual measurement and comparison and believes that the formula: $y = mx + b$ of Howland and Dana, is acurate for all classes of children. In this formula

y = surface area of child in sq. cm.
x = weight of child in gm.
$m = 0.483$
$b = 750$

Bailey and Murlin[30] found that not infrequently women have milk in their breasts on the first day of the puerperium, but the majority have only colostrum, estimated at 20 c.c. on the first day, increasing in amount on the second and third days, with the milk secretion appearing on the fourth day. In an analysis of colostrum the average for five samples was: Protein, 2.3; fat, 2.9; carbohydrate, 7.1; bomb calories, 67.7; physiologic heat values, calories, 65.3 in 100 c.c. The utilizable heat value of colostrum places it high as a food and possibly higher than breast milk when secretion is fully established. It is the ideal food for the new-born, the only trouble being there is too little of it. It is usually not until the fifth day that an energy supply of breast milk of 200 calories can be counted on. In only five instances out of twenty-eight different test periods were the respiratory quotients

29. Chapin, H. D.: Formula for the Determination of the Surface Area of Infants, Arch. Pediat. **31**:624 (Aug.) 1914.

30. Murlin, J. R.: Metabolism of the Mother and Offspring Before and After Parturition, Am. J. Obst. **75**:913, 1917.

of new-borns six hours of age above 0.90. Assuming that the oxygen absorption is normal at this early age, that is, is just rapid enough to meet the requirements of combustion, such a quotient would indicate the combustion of a considerable amount of glycogen. We know that the child born at term has in its liver a considerable store of this substance. The respiratory quotients obtained on the second day after birth indicate clearly that this reserve of glycogen is not sufficient to meet the needs of the patient for more than one day. In dry air the quotient was noticably higher than in moist air. At the end of the first week the quotient has returned to the expected level for whole milk diet, indicating that the various constituents are now present in sufficient amount to play their normal rôle in nutrition. The average heat production per hour for four babies who slept during the period of experiment is 6.73 calories, an average of 1.87 calory per kilogram of net body weight. The influence of crying on energy metabolism is shown by a child, 10 days old, when sleeping through observation period produced 8.14 calories per hour and while crying most of the time produced 10.73 calories, an increase of 31 per cent. Artificial food to supplement the scanty supply for newly born should contain 50 calories per kilogram for the first day, to be reduced as the natural supply comes forward.

Murlin[30] in his review of the literature on the metabolism of mother and offspring emphasized the independent behavior of the metabolism of the offspring from that of the mother. The low rate of metabolism immediately after birth is probably due to the fact that the heat regulating mechanism is not yet complete and the higher rate after the second or third month is doubtless related to the more active growth. An excellent bibliograph is attached.

Talbot[31] says that the total calories of the basal metabolism of the new-born infant may be calculated as follows: The total calories equal the length of the infant times 12.65 $\times$ the body surface. The energy requirement for the new-born infant is smaller per unit of body weight than for older infants. The respiratory quotient of the new-born infant indicates that the supply of glycogen in the body is quickly used up and that the energy is obtained in large part from body fat until breast milk is available. Chilling from exposure or a water bath depressed the metabolism; therefore the new-born infant should not be bathed in water and great care should be taken that it is not chilled. Weak or premature infants should be fed shortly after birth with milk of another mother when possible; when not, use a 5 per cent. solution of some sugar such as lactose as a temporary expedient.

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31. Talbot, F. B.: Physiology of the New-Born Infant, Am. J. Dis. **13**:495 (June) 1917.

Talbot[32] also reports the metabolism studies on a child having complete absence of the hemispheres of the brain. He was large for his age, being 8 months old. There was a large amount of subcutaneous fat, wth muscles relatively undeveloped. The child would remain absolutely quiet most of the time. His metabolism was very low.

The metabolism of the new-born infant, that is the energy transformed in a condition of repose and when the absorpton of food from the digestive tract is not going on, does not exceed 48 calories per kilogram of body weight per day.[33] Lusk believes that Huebner's figure of 100 calories per kilogram of body weight during the first month of infant nutrition is in excess of requirement; 80 calories is sufficient.

Careful examination of the saliva of the very young has shown that amylase is by no means always absent, but even if it were the possibilities of digestive utilization of starch are not limited to the efficiency of the saliva. Besides the salivary glands other structures, notably the pancreas, are sources of starch digesting ferments that need to be considered.[34]

Taylor[35] has described a cleverly contrived apparatus for the continuous and separate collection of saliva and gastric juice. He used this to obtain specimens of gastric juice from new-borns. As a result of his experiments he believes with Riche that there is no duodenal reflux into the infant's stomach. He was able to obtain gastric juice from starving infants in amounts that would indicate the possibility of a secretion of 200 c.c. daily. This juice is highly acid, containing both free and combined hydrochloric acid and pepsin. The acidity is often as high as in the secretions of the adult's stomachs. He administered various kinds of food into the mouth, no part of which, because of the previously mentioned apparatus, could reach the stomach, and there was no appetite or psychic secretion of gastric juice as a result.

Hess,[36] in his study of the gastric secretion in fifty-five infants from one-half to 18 hours old, found that they regularly secrete a considerable amount of hydrocloric acid before they are given food.

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32. Talbot, F. B., Energy Metabolism of Infant with Congenital Absence of Cerebral Hemispheres, Arch. Pediat. **32**:452 (June) 1915.

33. Editorial: Food Requirement in Infancy, J. A. M. A. **69**:1175 (Oct. 6) 1917.

34. Editorial: Starch Digestion in Early Life, J. A. M. A. **70**:1299 (May 4) 1918.

35. Taylor, Rood: Hunger and Appetite Secretion of Gastric Juice in Infants' Stomachs, Am. J. Dis. Child. **14**:258 (Oct.) 1917.

36. Hess, A. F.: Gastric Secretion of Infants at Birth, Am. J. Dis. Child. **6**:264, 1913.

The amount varies greatly. Renin, pepsin, and lipase are also found to be present. He observes that it is hard to account for the gastric secretion immediately after birth without stimulation and believes it may be prenatal. He suggests that the high acidity may at times be related to the presence of pylorospasm or to duodenal ulcer met with in infancy. Duodenal and pancreatic secretion is very slight in the newly born.

Taylor[37] reports the results of an extensive study of what he terms "hunger contractions" in five premature and forty full-term new-born infants. Work on several older children is also included in his report. The hunger contractions of the new-born child prove to be greater than in older ones and are not inhibited by introducing food into the mouth. Reflex inhibition from the presence of food in the stomach is present in infants of all ages. Hunger is not believed to be an ordinary cause of crying in the normally developing breast fed baby. Time of development of hunger after feeding in healthy infants gaining in weight and receiving a sufficient amount of food is as follows: for premature infants under 1 month, 1 hour and 40 minutes, in full term infants under 2 weeks, 2 hours and 50 minutes, in infants from 2 weeks to 4 months, 3 hours and 40 minutes. Time required for development of hunger in infants with chronic nourishment disturbance or those receiving poorly tolerated food is shorter than in normal infants, occurring many times while the food from the previous meal is still in the stomach.

Copeland[38] believes the deficiency in development of the new-born anatomically and physiologically is often responsible for otherwise unexplained rises in temperature, the instability of the nervous system being demonstrated in the abnormal responses of the heat regulating mechanism. His article covers a variety of other causes of fever in older children, and he observes that otitis media is present in many cases in the very young and may be one obscure cause of these early fevers.

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37. Taylor, Rood: Hunger in the Infant, Am. J. Dis. Child. **14**:233 (Oct.) 1917.

38. Copeland, E. P.: Fever of Obscure Causation in Infancy and Early Childhood, J. A. M. A. **67**:1346 (Nov. 4) 1916.

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